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(54) Title: XENOBIOTIC DETOXIFICATION GENE FROM PLANTS (57) Abstract A novel plant gene is provided, which is a member of the <i>mdr</i> family of genes encoding ABC transporters. The gene is inducible by NPPB, and is preferentially expressed in roots upon induction. The gene is useful for detoxification of certain xenobiotics to protect plants from the detrimental effects of such compounds. Also provided are plants that over-express and under-express this <i>mdr</i> gene.		

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XENOBIOTIC DETOXIFICATION GENE FROM PLANTS

This application claims priority to U.S. 60/101,814, filed September 25, 1998, the entirety of which is incorporated by reference herein.

5 Pursuant to 35 U.S.C. §202(c), it is acknowledged that the U.S. Government has certain rights in the invention described herein, which was made in part with funds from the National Science Foundation, Grant No. IBN-9416016.

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FIELD OF THE INVENTION

This invention relates to the field of stress resistance in plants. In particular, the invention provides a novel gene from plants, which encodes an MDR-
15 like ABC transporter, involved in detoxification of certain xenobiotics to protect plants from their detrimental effects.

BACKGROUND OF THE INVENTION

20 Several publications are referenced in this application to describe the state of the art to which the invention pertains. Each of these publications is incorporated by reference herein.

Environmental stress is one of the most
25 important limitations on plant productivity, growth and survival. An ever-increasing source of environmental stress to plants is the stress caused by environmental pollutants in the soil, water and atmosphere. Such pollutants include herbicides, pesticides and related
30 agronomic products, as well as organic and inorganic waste material from industry and other sources. Other toxic agents that threaten the survival of plants include various toxins produced by epiphytic or soilborne

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microorganisms, such as fungi and bacteria.

In order to survive in toxic environments, plants must have mechanisms to detoxify xenobiotics, heavy metals and other toxic compounds. This generally involves modification of the toxic compound and subsequent excretion into the vacuole or apoplastic space. Recently, certain ATP-binding cassette (ABC) transporters have been identified in plants, which appear to be involved in the detoxification process.

The ABC transporter family is very large, with representatives existing in many different classes of organisms. Two well studied groups of ABC transporters, encoded by *mdr* and *mrp* genes, respectively, are associated with the multi-drug resistance phenomenon observed in mammalian tumor cells. The *mdr* genes encode a family of P-glycoproteins that mediate the energy-dependent efflux of certain lipophilic drugs from cells. The *mrp* genes encode a family of transporters that mediate the extrusion of a variety of organic compounds after their conjugation with glutathione. *YCF1*, the yeast homolog of *mrp*, encodes a protein capable of glutathione-mediated detoxification of heavy metals.

Homologs of *mrp* and *mdr* genes have been identified in plant species. In *Arabidopsis thaliana*, the glutathione-conjugate transporter encoded by the *mrp* homolog is located in the vacuolar membrane and is responsible for sequestration of xenobiotics in the central vacuole (Tommasini et al., FEBS Lett. 411: 206-210, 1997; Li et al., Plant Physiol. 107: 1257-1268, 1995). An *mdr*-like gene (*atpgp1*) has also been identified in *A. thaliana*, which encodes a putative P-glycoprotein homolog. The *atpgp1* gene was found to share significant sequence homology and structural organization with human *mdr* genes, and was expressed with particular

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abundance in inflorescence axes (Dudler & Hertig, J. Biol. Chem. 267: 5882-5888, 1992). Other MDR homologs have been found in potato (Wang et al., Plant Mol. Biol. 31: 683, 1996) and barley (Davies et al., Gene 199: 195, 5 1997).

The aforementioned *mrp* and *mdr* plant homologs were identified as a result of an effort to understand the molecular basis for development in plants of cross-resistance to herbicides of unrelated classes. However, 10 these transporters are likely to serve the more general role in plants of sequestering, secreting, or otherwise detoxifying various organic and inorganic xenobiotics. Accordingly, it will constitute an advance in the art of plant genetic engineering of stress tolerance to identify 15 and characterize other members of this class of transporters in plants.

SUMMARY OF THE INVENTION

In accordance with the present invention, a new 20 plant *mdr* homolog has been identified. Unlike the previously identified plant *mdr* homologs, this new gene is inducible by a class of compounds known to inhibit chloride ion channels.

According to one aspect of the invention, a 25 nucleic acid isolated from a plant is provided, which encodes a p-glycoprotein that is inducible by exposure of the plant to NPPB. The isolated nucleic acid is preferentially expressed in plant roots upon exposure of the plant to NPPB. In a preferred embodiment, the plant 30 from which the nucleic acid is isolated is selected from the group consisting of *Brassica napus* and *Arabidopsis thaliana* and is 3850-4150 nucleotides in length. In a more preferred embodiment, the nucleic acid has the restriction sites shown in Figure 4 for at least three

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restriction enzymes. In particularly preferred
embodiments, the nucleic acid molecule encodes a
polypeptide having SEQ ID NO:2. In an exemplary
embodiment, the nucleic acid is a cDNA comprising the
5 coding region of SEQ ID NO:1 or SEQ ID NO:10.

According to another aspect of the invention is
an expression cassette that comprises a pLPAC gene
operably linked to a promoter, and in a more preferred
embodiment the pLPAC gene is from *Arabidopsis*. In
10 preferred embodiments, the expression cassette comprises
the cauliflower mosaic virus 35S promoter, and part of
all of SEQ ID NO:1 or SEQ ID NO:10. Further included in
this aspect is a vector comprising the expression
cassette and a method for producing transgenic plants
15 with the expression cassette and vector.

Another aspect of the invention are transgenic
cells and plants containing the nucleic acids of the
invention. In one preferred embodiment, the nucleic
acids are be in the aforementioned expression cassette.
20 Further included in this aspect are reproductive units
from the transgenic plant.

According to another aspect of the invention,
an isolated nucleic acid molecule is provided, which has
a sequence selected from the group consisting of: a) SEQ
25 ID NO:1 and SEQ ID NO:10; b) a nucleic acid sequence
that is at least about 60% homologous to the coding
regions of SEQ ID NO:1 or SEQ ID NO:10; c) a sequence
hybridizing with SEQ ID NO:1 or SEQ ID NO:10 at moderate
stringency; d) a sequence encoding part or all of a
30 polypeptide having SEQ ID NO:2; e) a sequence encoding an
amino acid sequence that is at least about 70% identical
to SEQ ID NO:2; f) a sequence encoding an amino acid
sequence that is at least about 80% similar to SEQ ID
NO:2; g) a sequence encoding an amino acid sequence that

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is at least about 40% similar to residues 1-76, 613-669 or 1144-1161 of SEQ ID NO:2; and h) a sequence hybridizing at moderate stringency to a sequence encoding residues 1-76, 613-669 or 1144-1161 of SEQ ID NO:2. A
5 polypeptide produced by expression of the above listed sequences is also provided.

According to another aspect of the invention, an isolated plant p-glycoprotein, which is inducible upon exposure of the plant to NPPB, is provided. The
10 polypeptide preferably confers upon a cell in which it is found resistance to Rhodamine 6G. The polypeptide is preferentially produced in roots upon the exposure to the NPPB. The polypeptide is preferably from *Brassica napus* or *Arabidopsis thaliana*. In most preferred embodiments,
15 the polypeptide has a sequence that is a) an amino acid sequence that is at least 80% similar to SEQ ID NO:2; b) an amino acid sequence that is at least 70% identical to SEQ ID NO:2; c) an amino acid sequence that is at least 40% similar to residues 1-76, 613-669 or 1144-1161 of SEQ
20 ID NO:2; and d) an amino acid sequence encoded by a nucleic acid sequence hybridizing at moderate stringency to a amino acid sequence encoding residues 1-76, 613-669 or 1144-1161 of SEQ ID NO:2.

According to other aspects of the invention,
25 antibodies immunologically specific for the polypeptides of the invention are provided, that immunologically specific to any of the polypeptides, of polypeptide encoded by the nucleic acids of the invention. In a preferred embodiment, the antibody is immunospecific to
30 residues 1-76, 613-669 or 1144-1161 of SEQ ID NO:2.

According to another aspect of the invention, a plant p-glycoprotein gene promoter, which is inducible by NPPB, is also provided. In a preferred embodiment, the promoter is part or all of residues 1-3429 of SEQ ID

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NO:10.

According to another aspect of the invention, plants that have reduces levels of *plPAC* protein are provided. In a preferred embodiment, these plants have mutations in the *plPAC* gene, and in a particularly preferred embodiment, the *plPAC* gene is mutated due to the insertion of a T-DNA. Also provided with this aspect is a method for selecting plants with mutations in *plPAC* using SEQ ID NOS:11-14 as PCR primers.

These and other features and advantages of the present invention will be described in greater detail in the description and examples set forth below.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Amino acid sequence lineup of *ATPAC* deduced amino acid sequence and the amino acid sequences of related mammalian and plant genes. The lineup shows the *ATPAC* deduced amino acid sequence (SEQ ID NO:2) compared with (1) *hmdr1* (SEQ ID NO:3); (2) *mmdr1* (SEQ ID NO: 4); (3) *hmdr3* (SEQ ID NO:5); (4) *mmdr2* (SEQ ID NO:6); (5) *atpgp1* (SEQ ID NO:7); and (6) *atpgp2* (SEQ ID NO:8). A consensus sequence (SEQ ID NO: 9) is also shown.

Figure 2. Graph depicting the effect of rhodamine 6G on the growth rate of cells transformed with and expressing *ATPAC* as compared with control cells not containing *ATPAC*.

Figure 3. Restriction map of genomic clone of *ATPAC*, SEQ ID NO:10.

Figure 4. Restriction map of cDNA clone of *ATPAC*, SEQ ID NO:1.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

Various terms relating to the biological

molecules of the present invention are used hereinabove and also throughout the specification and claims.

5 invention, the term "isolated nucleic acid" is sometimes used. This term, when applied to DNA, refers to a DNA molecule that is separated from sequences with which it is immediately contiguous (in the 5' and 3' directions) in the naturally occurring genome of the organism from which it was derived. For example, the "isolated nucleic acid" may comprise a DNA molecule inserted into a vector, such as a plasmid or virus vector, or integrated into the genomic DNA of a procaryote or eucaryote. An "isolated nucleic acid molecule" may also comprise a cDNA molecule.

10 With respect to RNA molecules of the invention, the term "isolated nucleic acid" primarily refers to an RNA molecule encoded by an isolated DNA molecule as defined above. Alternatively, the term may refer to an RNA molecule that has been sufficiently separated from RNA molecules with which it would be associated in its natural state (i.e., in cells or tissues), such that it exists in a "substantially pure" form (the term "substantially pure" is defined below).

15 Nucleic acid sequences and amino acid sequences can be compared using computer programs that align the similar sequences of the nucleic acid sequences and amino acid sequences to define the differences. For purposes of this invention, the DNASTar program (DNASTar, Inc., Madison, Wisconsin) and the default parameters used by that program are the parameters intended to be used herein to compare sequence identity and similarity. Alternately, the Blastn and Blastp 2.0 programs provided by the National Center for Biotechnology Information (at <http://www.ncbi.nlm.nih.gov/blast/>; Altschul et al., 1990, J Mol Biol 215:403-410) using a gapped alignment

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with default parameters, may be used to determine the level of identity and similarity between nucleic acid sequences and amino acid sequences.

The term "substantially the same" refers to
5 nucleic acid or amino acid sequences having sequence variation that do not materially affect the nature of the protein (i.e. the structure, thermostability characteristics and/or biological activity of the protein). With particular reference to nucleic acid
10 sequences, the term "substantially the same" is intended to refer to the coding region and to conserved sequences governing expression, and refers primarily to degenerate codons encoding the same amino acid, or alternate codons encoding conservative substitute amino acids in the
15 encoded polypeptide. With reference to amino acid sequences, the term "substantially the same" refers generally to conservative substitutions and/or variations in regions of the polypeptide not involved in determination of structure or function.

20 The terms "percent identical" and "percent similar" are also used herein in comparisons among amino acid and nucleic acid sequences. When referring to amino acid sequences, "percent identical" refers to the percent of the amino acids of the subject amino acid sequence
25 that have been matched to identical amino acids in the compared amino acid sequence by a sequence analysis program. "Percent similar" refers to the percent of the amino acids of the subject amino acid sequence that have been matched to identical or conserved amino acids.
30 Conserved amino acids are those which differ in structure but are similar in physical properties such that the exchange of one for another would not appreciably change the tertiary structure of the resulting protein. Conservative substitutions are defined in Taylor (1986,

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J. Theor. Biol. 119:205). When referring to nucleic acid molecules, "percent identical" refers to the percent of the nucleotides of the subject nucleic acid sequence that have been matched to identical nucleotides by a sequence analysis program.

With respect to protein, the term "isolated protein" or "isolated and purified protein" is sometimes used herein. This term refers primarily to a protein produced by expression of an isolated nucleic acid molecule of the invention. Alternatively, this term may refer to a protein which has been sufficiently separated from other proteins with which it would naturally be associated, so as to exist in "substantially pure" form.

The term "substantially pure" refers to a preparation comprising at least 50-60% by weight the compound of interest (e.g., nucleic acid, oligonucleotide, protein, etc.). More preferably, the preparation comprises at least 75% by weight, and most preferably 90-99% by weight, the compound of interest. Purity is measured by methods appropriate for the compound of interest (e.g. chromatographic methods, agarose or polyacrylamide gel electrophoresis, HPLC analysis, and the like).

With respect to antibodies of the invention, the term "immunologically specific" refers to antibodies that bind to one or more epitopes of a protein of interest, but which do not substantially recognize and bind other molecules in a sample containing a mixed population of antigenic biological molecules.

With respect to oligonucleotides, the term "specifically hybridizing" refers to the association between two single-stranded nucleotide molecules of sufficiently complementary sequence to permit such hybridization under pre-determined conditions generally

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used in the art (sometimes termed "substantially complementary"). In particular, the term refers to hybridization of an oligonucleotide with a substantially complementary sequence contained within a single-stranded DNA or RNA molecule of the invention, to the substantial
5 exclusion of hybridization of the oligonucleotide with single-stranded nucleic acids of non-complementary sequence.

The term "expression cassette", as used herein,
10 comprises 5' and 3' regulatory regions operably linked to a coding sequence. The coding sequence may be in the sense or antisense orientation with respect to the 5' regulatory region.

The term "promoter region" refers to the 5'
15 regulatory regions of a gene.

The term "reporter gene" refers to genetic sequences which may be operably linked to a promoter region forming a transgene, such that expression of the reporter gene coding region is regulated by the promoter
20 and expression of the transgene is readily assayed.

The term "selectable marker gene" refers to a gene product that when expressed confers a selectable phenotype, such as antibiotic resistance, on a transformed cell or plant.

25 The term "operably linked" means that the regulatory sequences necessary for expression of the coding sequence are placed in the DNA molecule in the appropriate positions relative to the coding sequence so as to effect expression of the coding sequence. This
30 same definition is sometimes applied to the arrangement of coding sequences and transcription control elements (e.g. promoters, enhancers, and termination elements) in an expression vector.

The term "DNA construct" refers to genetic

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sequence used to transform plants and generate progeny transgenic plants. These constructs may be administered to plants in a viral or plasmid vector. Other methods of delivery such as Agrobacterium T-DNA mediated transformation and transformation using the biolistic process are also contemplated to be within the scope of the present invention. The transforming DNA may be prepared according to standard protocols such as those set forth in "Current Protocols in Molecular Biology", eds. Frederick M. Ausubel et al., John Wiley & Sons, 1995.

The term "xenobiotic" refers to foreign chemicals or agents not produced or naturally found in the organism. The term is commonly used in reference to toxic or otherwise detrimental foreign chemicals, such as organic pollutants or heavy metals.

II. Description of *plPAC* and its Encoded Polypeptide

In accordance with the present invention, a nucleic acid encoding a novel ATP-binding-cassette (ABC) transporter has been isolated and cloned from plants. The nucleic acid is referred to herein as *plPAC*.

A cDNA clone of the *plPAC* from *Arabidopsis thaliana*, an exemplary *plPAC* of the invention, is described in detail herein and its nucleotide sequence is set forth in Example 1 as SEQ ID NO:1. This nucleic acid molecule is referred to as "ATPAC". It is 36% identical and 51% similar to human *mdr1* across the entire sequence. It is 51% identical to the *atpgp1* gene reported by Dudler & Hertig (1997, *supra*) and 50% identical to *atpgp2*, a close homolog of *atpgp1*, published in the Genbank database. ATPAC protein is 65% similar to *atpgp1* and *atpgp2* proteins.

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A partial clone of a *p*LPAC of the invention was originally isolated from *Brassica napus* via differential expression screening of plants grown in the presence or absence of the chloride channel blocker, 5-nitro-2-(3-phenylpropylamino) benzoic acid (NPPB). A 0.5 kb gene fragment was identified, which had been up-regulated in response to NPPB treatment. This cDNA fragment was used to screen an *Arabidopsis* cDNA library, from which the complete ATPAC clone was isolated. The isolation and characterization of ATPAC is described in Example 1.

A genomic clone of ATPAC (SEQ ID NO:10) has also been isolated from a bacterial artificial chromosome (BAC) library of the *Arabidopsis* genome (BAC clone IGF F3J22, obtained from the *Arabidopsis* stock center, Ohio State University). A 7 kb fragment containing part of ATPAC and additional 5' regulatory sequences was subcloned into a plasmid vector (pBluescript). A restriction map of ATPAC is found in Fig. 3. The corresponding cDNA clone of ATPAC is found in SEQ ID NO:1 and its restriction map is Fig. 4.

Among the unique features of this nucleic acid molecule as compared with other *mdr*-like genes from plants are its inducibility by certain compounds, including NPPB and herbicides, and its preferential expression in roots. The promoter regulatory region of ATPAC comprises residues 1-3429 of SEQ ID NO:10.

Although the ATPAC cDNA clone from *Arabidopsis thaliana* is described and exemplified herein, this invention is intended to encompass nucleic acid sequences and proteins from other plant species that are sufficiently similar to be used instead of ATPAC nucleic acid and proteins for the purposes described below. These include, but are not limited to, allelic variants and natural mutants of SEQ ID NO:1, which are likely to

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be found in different species of plants or varieties of *Arabidopsis*.

Because such variants are expected to possess certain differences in nucleotide and amino acid sequence, this invention provides an isolated *plPAC* nucleic acid molecule having at least about 60% (preferably 70% and more preferably over 80%) sequence homology in the coding regions with the nucleotide sequence set forth as SEQ ID NO:1 or SEQ ID NO:10 (and, most preferably, specifically comprising the coding region of SEQ ID NO:1). Also provided are nucleic acids that encode a polypeptide that is at least about 40% (preferably 50% and most preferably 60%) similar to residues 1-76, 613-669 or 1144-1161 of SEQ ID NO:2. Also provided are nucleic acids that hybridize to the nucleic acids of SEQ ID NO:1, SEQ ID NO:10, or nucleic acids encoding the regions of residues 1-76, 613-669 or 1144-1161 of SEQ ID NO:2, preferably under moderate stringency (more preferably, high stringency, and most preferably, very high stringency).

In other preferred embodiments, the nucleic acids have a restriction digest map that is identical for at least 3 enzymes (more preferably 6 enzymes and most preferably 9 enzymes) to the maps shown in Figs. 3 or 4. In another preferred embodiment, the nucleic acids have a restriction digest map identical to those shown in Fig. 3 for enzymes *XhoI*, *XcmI* and *SpeI* (preferably additionally *SacI*, *PacI* and *BsaI*, and most preferably additionally *AclI*, *BanI* and *SnaBI*). In another preferred embodiment, the nucleic acids have a restriction digest map identical to those shown in Fig. 4 for enzymes *XbaI*, *TatI* and *NciI* (preferably additionally *DraI*, *BsmI* and *BclI*, and most preferably additionally *AccI*, *BsgI* and *TliI*). The nucleic acids of the invention are at least 20 nucleic

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acids in length (preferably at least 50 nucleic acids and most preferably at least 100 nucleic acids).

In accordance with the invention, novel *plPAC* genes from two plant species, *Brassica napus* and
5 *Arabidopsis thaliana*, are presented. This constitutes the first description of this unique p-glycoprotein in plants. Indeed, the closest known protein sequence, also from *Arabidopsis*, is only 65% identical suggesting that the *ATPAC* gene is novel and is expected to have novel
10 properties. The isolation of two *plPAC* genes from different species enables the isolation of further *plPAC* genes from other plant species. Isolated nucleic acids that are *plPAC* genes from any plant species are considered part of the instant invention. In particular,
15 the nucleic acids of other *plPAC* genes can be isolated using sequences of *ATPAC* that distinguish *plPAC* genes from other plant *mdr* genes according to methods that are well known to those in the art of gene isolation. In particular, sequences that encode residues 1-76, 613-669
20 and 1144-1161 of SEQ ID NO:2 can be used. In a preferred embodiment, the *plPAC* gene is from any higher plant species (more preferred from a dicot species, and most preferred from a species in Brassicaceae (or Cruciferae)).

25 This invention also provides isolated polypeptide products of the open reading frames of SEQ ID NO:1 or SEQ ID NO:10, having at least about 70% (preferably 80% and most preferably 90%) sequence identity, or at least about 80% similarity (preferably
30 90% and more preferably 95%) with the amino acid sequence of SEQ ID NO:2. In another embodiment, the polypeptides of the invention are at least about 40% identical (preferably 50%, and most preferably 60%) to the regions of residues 1-76, 613-669 or 1144-1161 of SEQ ID NO:2.

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Because of the natural sequence variation likely to exist among *plPAC* genes, one skilled in the art would expect to find up to about 30-40% nucleotide sequence variation, while still maintaining the unique properties of the *plPAC* gene and encoded polypeptide of the present invention. Such an expectation is due in part to the degeneracy of the genetic code, as well as to the known evolutionary success of conservative amino acid sequence variations, which do not appreciably alter the nature of the encoded protein. Accordingly, such variants are considered substantially the same as one another and are included within the scope of the present invention.

Also provided are transgenic plants transformed with part or all of the nucleic acids of the invention. Transgenic plants that over-express a *plPAC* coding sequence are one embodiment of this aspect of the invention. Example 3 provides for one prototype of such a plant. In a preferred embodiment, the *ATPAC* gene is used, and in a most preferred embodiment SEQ ID NO:1 or SEQ ID NO:10 is used. The *plPAC* gene may be placed under a powerful constitutive promoter, such as the Cauliflower Mosaic Virus (CaMV) 35S promoter or the figwort mosaic virus 35S promoter. In a preferred embodiment, the 35SCaMV promoter is used. Transgenic plants expressing the *plPAC* gene under an inducible promoter (either its own promoter or a heterologous promoter) are also contemplated to be within the scope of the present invention. Inducible plant promoters include the tetracycline repressor/operator controlled promoter. In a preferred embodiment, a native *plPAC* promoter is used, and in a most preferred embodiment, residues 1-3429 of SEQ ID NO:10 is used. Plant species that are contemplated for overexpression of a *plPAC* coding sequence include, but are not limited to, soybean.

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In another embodiment, overexpression of *plPAC* is induced to generate a co-suppression effect. This excess expression serves to promote down-regulation of both endogenous and exogenous *plPAC* genes.

5 In some instances, it may be desirable to down-regulate or inhibit expression of endogenous *plPAC* in plants possessing the gene. Accordingly, *plPAC* nucleic acid molecules, or fragments thereof, may also be utilized to control the production of *plPAC*-encoded P-glycoproteins. In one embodiment, full-length *plPAC* antisense molecules or antisense oligonucleotides, targeted to specific regions of *plPAC*-encoded RNA that are critical for translation, are used. The use of antisense molecules to decrease expression levels of a pre-determined gene is known in the art. In a preferred
10 embodiment, antisense molecules are provided *in situ* by transforming plant cells with a DNA construct which, upon transcription, produces the antisense sequences. Such constructs can be designed to produce full-length or partial antisense sequences. One example of antisense *plPAC* transgenic plants is given in Example 3.

In another embodiment, knock-out plants are obtained by screening a T-DNA mutagenized plant population for insertions in the *plPAC* gene (see Krysan
25 et al., 1996, PNAS 93:8145). One example of this embodiment of the invention is found in Example 3. Optionally, transgenic plants can be created containing mutations in the region encoding the active site of *plPAC*. These last two embodiments are preferred over the use of anti-sense constructs due to the high homology
30 among P-glycoproteins.

The promoter of *ATPAC* is also provided in accordance with the invention. This promoter has the useful properties of root expression and inducability by

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NPPB. The prototypic example of this aspect of the invention is residues 1-3429 of SEQ ID NO:10. It is anticipated that *plPAC* genes from other plant species will likewise exhibit the aforementioned useful properties. As these promoter regions can easily be isolated from the *plPAC* genes that are provided with the invention, all plant *plPAC* gene promoters are provided with the invention. The nucleic acids of the invention therefore include a nucleic acid molecule that is at least about 70% identical (preferably 80% and most preferably 90%) to the residues 1-3429 of SEQ ID NO:10. Also provided are nucleic acids that hybridize to the nucleic acid residues 1-3429 of SEQ ID NO:10 preferably under moderate stringency (more preferably, high stringency, and most preferably, very high stringency).

The present invention also provides antibodies capable of immuno-specifically binding to polypeptides of the invention. Polyclonal or monoclonal antibodies directed toward any of the peptides encoded by *plPAC* may be prepared according to standard methods. Monoclonal antibodies may be prepared according to general methods of Köhler and Milstein, following standard protocols. In a preferred embodiment, antibodies are prepared, which react immuno-specifically with various epitopes of the *plPAC*-encoded polypeptides. In a preferred embodiment, the antibodies are immunologically specific to the polypeptide of residues 1-76, 613-669 or 1144-1161 of SEQ ID NO:2.

The following description sets forth the general procedures involved in practicing the present invention. To the extent that specific materials are mentioned, it is merely for purposes of illustration and is not intended to limit the invention. Unless otherwise specified, general cloning procedures, such as those set

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forth in Sambrook et al., Molecular Cloning, Cold Spring Harbor Laboratory (1989) (hereinafter "Sambrook et al.") or Ausubel et al. (eds) Current Protocols in Molecular Biology, John Wiley & Sons (1997) (hereinafter "Ausubel et al.") are used.

III. Preparation of *PlPAC* Nucleic Acid Molecules, encoded Polypeptides, Antibodies Specific for the Polypeptides and Transgenic Plants

1. Nucleic Acid Molecules

PlPAC nucleic acid molecules of the invention may be prepared by two general methods: (1) they may be synthesized from appropriate nucleotide triphosphates, or (2) they may be isolated from biological sources. Both methods utilize protocols well known in the art.

The availability of nucleotide sequence information, such as the cDNA having SEQ ID NO:1, enables preparation of an isolated nucleic acid molecule of the invention by oligonucleotide synthesis. Synthetic oligonucleotides may be prepared by the phosphoramidite method employed in the Applied Biosystems 38A DNA Synthesizer or similar devices. The resultant construct may be purified according to methods known in the art, such as high performance liquid chromatography (HPLC). Long, double-stranded polynucleotides, such as a DNA molecule of the present invention, must be synthesized in stages, due to the size limitations inherent in current oligonucleotide synthetic methods. Thus, for example, a long double-stranded molecule may be synthesized as several smaller segments of appropriate complementarity. Complementary segments thus produced may be annealed such that each segment possesses appropriate cohesive termini for attachment of an adjacent segment. Adjacent segments may be ligated by annealing cohesive termini in the

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presence of DNA ligase to construct an entire long double-stranded molecule. A synthetic DNA molecule so constructed may then be cloned and amplified in an appropriate vector.

5 *PlPAC* genes also may be isolated from appropriate biological sources using methods known in the art. In fact, the *ATPAC* clone was isolated from an *Arabidopsis* cDNA library using a partial clone obtained from *Brassica napus*. In alternative embodiments, genomic
10 clones of *plPAC* may be isolated.

In accordance with the present invention, nucleic acids having the appropriate level sequence homology with part or all the coding regions of SEQ ID NO:1 or SEQ ID NO:10 may be identified by using
15 hybridization and washing conditions of appropriate stringency. For example, hybridizations may be performed, according to the method of Sambrook et al., using a hybridization solution comprising: 5X SSC, 5X Denhardt's reagent, 1.0% SDS, 100 µg/ml denatured,
20 fragmented salmon sperm DNA, 0.05% sodium pyrophosphate and up to 50% formamide. Hybridization is carried out at 37-42°C for at least six hours. Following hybridization, filters are washed as follows: (1) 5 minutes at room temperature in 2X SSC and 1% SDS; (2) 15 minutes at room
25 temperature in 2X SSC and 0.1% SDS; (3) 30 minutes-1 hour at 37°C in 2X SSC and 0.1% SDS; (4) 2 hours at 45-55° in 2X SSC and 0.1% SDS, changing the solution every 30 minutes.

One common formula for calculating the
30 stringency conditions required to achieve hybridization between nucleic acid molecules of a specified sequence homology (Sambrook et al., 1989):

$$T_m = 81.5^{\circ}\text{C} + 16.6\text{Log} [\text{Na}^+] + 0.41(\% \text{G+C}) - 0.63 (\% \text{formamide}) - 600/\text{\#bp in duplex}$$

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As an illustration of the above formula, using $[N+] = [0.368]$ and 50% formamide, with GC content of 42% and an average probe size of 200 bases, the T_m is 57°C. The T_m of a DNA duplex decreases by 1 - 1.5°C with every 1% decrease in homology. Thus, targets with greater than about 75% sequence identity would be observed using a hybridization temperature of 42°C.

The stringency of the hybridization and wash depend primarily on the salt concentration and temperature of the solutions. In general, to maximize the rate of annealing of the probe with its target, the hybridization is usually carried out at salt and temperature conditions that are 20-25°C below the calculated T_m of the of the hybrid. Wash conditions should be as stringent as possible for the degree of identity of the probe for the target. In general, wash conditions are selected to be approximately 12-20°C below the T_m of the hybrid. In regards to the nucleic acids of the current invention, a moderate stringency hybridization is defined as hybridization in 6X SSC, 5X Denhardt's solution, 0.5% SDS and 100 µg/ml denatured salmon sperm DNA at 42°C, and wash in 2X SSC and 0.5% SDS at 55°C for 15 minutes. A high stringency hybridization is defined as hybridization in 6X SSC, 5X Denhardt's solution, 0.5% SDS and 100 µg/ml denatured salmon sperm DNA at 42°C, and wash in 1X SSC and 0.5% SDS at 65°C for 15 minutes. A very high stringency hybridization is defined as hybridization in 6X SSC, 5X Denhardt's solution, 0.5% SDS and 100 µg/ml denatured salmon sperm DNA at 42°C, and wash in 0.1X SSC and 0.5% SDS at 65°C for 15 minutes.

Nucleic acids of the present invention may be maintained as DNA in any convenient cloning vector. In a preferred embodiment, clones are maintained in plasmid

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cloning/expression vector, such as pGEM-T (Promega Biotech, Madison, WI) or pBluescript (Stratagene, La Jolla, CA), either of which is propagated in a suitable *E. coli* host cell.

5 *plPAC* nucleic acid molecules of the invention include cDNA, genomic DNA, RNA, and fragments thereof which may be single- or double-stranded. Thus, this invention provides oligonucleotides (sense or antisense strands of DNA or RNA) having sequences capable of
10 hybridizing with at least one sequence of a nucleic acid molecule of the present invention, such as selected segments of SEQ ID NO:1 or SEQ ID NO:10. Such oligonucleotides are useful as probes for detecting *plPAC* genes or mRNA in test samples, e.g. by PCR amplification,
15 mapping of genes or for the positive or negative regulation of expression of *plPAC* genes at or before translation of the mRNA into proteins.

The *plPAC* promoter is also expected to be useful in connection with the present invention, inasmuch
20 as it is inducible in plants upon exposure to anion channel blockers. As mentioned above, seven-kilobase fragment of genomic DNA has been isolated, which contains part or all of the *plPAC* promoter from *Arabidopsis thaliana*. This promoter can be used in chimeric gene
25 constructs to facilitate inducible expression of any coding sequence of interest, upon exposure to NPPB or similar-acting compounds.

2. Proteins

30 Polypeptides encoded by *plPAC* nucleic acids of the invention may be prepared in a variety of ways, according to known methods. If produced *in situ* the polypeptides may be purified from appropriate sources, e.g., plant roots or other plant parts.

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Alternatively, the availability of nucleic acid molecules encoding the polypeptides enables production of the proteins using *in vitro* expression methods known in the art. For example, a cDNA or gene may be cloned into an appropriate *in vitro* transcription vector, such as pSP64 or pSP65 for *in vitro* transcription, followed by cell-free translation in a suitable cell-free translation system, such as wheat germ or rabbit reticulocytes. *In vitro* transcription and translation systems are commercially available, e.g., from Promega Biotech, Madison, Wisconsin or BRL, Rockville, Maryland.

According to a preferred embodiment, larger quantities of plPAC-encoded polypeptide may be produced by expression in a suitable procaryotic or eucaryotic system. For example, part or all of a DNA molecule, such as the cDNA having SEQ ID NO:1, may be inserted into a plasmid vector adapted for expression in a bacterial cell (such as *E. coli*) or a yeast cell (such as *Saccharomyces cerevisiae*), or into a baculovirus vector for expression in an insect cell. Such vectors comprise the regulatory elements necessary for expression of the DNA in the host cell, positioned in such a manner as to permit expression of the DNA in the host cell. Such regulatory elements required for expression include promoter sequences, transcription initiation sequences and, optionally, enhancer sequences.

The plPAC polypeptide produced by gene expression in a recombinant procaryotic or eucaryotic system may be purified according to methods known in the art. In a preferred embodiment, a commercially available expression/secretion system can be used, whereby the recombinant protein is expressed and thereafter secreted from the host cell, to be easily purified from the surrounding medium. If expression/secretion vectors are

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not used, an alternative approach involves purifying the recombinant protein by affinity separation, such as by immunological interaction with antibodies that bind specifically to the recombinant protein. Such methods are commonly used by skilled practitioners.

The *plPAC*-encoded polypeptides of the invention, prepared by the aforementioned methods, may be analyzed according to standard procedures.

10 C. Transgenic Plants

Transgenic plants expressing the *plPAC* gene can be generated using standard plant transformation methods known to those skilled in the art. These include, but are not limited to, *Agrobacterium* vectors, PEG treatment of protoplasts, biolistic DNA delivery, UV laser microbeam, gemini virus vectors, calcium phosphate treatment of protoplasts, electroporation of isolated protoplasts, agitation of cell suspensions with microbeads coated with the transforming DNA, direct DNA uptake, liposome-mediated DNA uptake, and the like. Such methods have been published in the art. See, e.g., Methods for Plant Molecular Biology (Weissbach & Weissbach, eds., 1988); Methods in Plant Molecular Biology (Schuler & Zielinski, eds., 1989); Plant Molecular Biology Manual (Gelvin, Schilperoort, Verma, eds., 1993); and Methods in Plant Molecular Biology - A Laboratory Manual (Maliga, Klessig, Cashmore, Gruissem & Varner, eds., 1994).

The method of transformation depends upon the plant to be transformed. The biolistic DNA delivery method is useful for nuclear transformation. In another embodiment of the invention, *Agrobacterium* vectors are used to advantage for efficient transformation of plant nuclei.

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In a preferred embodiment, the gene is introduced into plant nuclei in *Agrobacterium* binary vectors. Such vectors include, but are not limited to, BIN19 (Bevan, 1984, Nucleic Acid Res 12: 8711-8721) and derivatives thereof, the pBI vector series (Jefferson et al., 1987, PNAS 83:8447-51), and binary vectors pGA482 and pGA492 (An, 1986) and others (for review, see An, 1995, Methods Mol Biol 44:47-58). In preferred embodiments, the pPZP211 vector (Hajdukiewicz et al., 1994, PMB 25:989-994) or PCGN7366 (Calgene, CA) are used. DNA constructs for transforming a selected plant comprise a coding sequence of interest operably linked to appropriate 5' (e.g., promoters and translational regulatory sequences) and 3' regulatory sequences (e.g., terminators).

Using an *Agrobacterium* binary vector system for transformation, the *plPAC* coding region, under control of a constitutive or inducible promoter as described above, is linked to a nuclear drug resistance marker, such as kanamycin resistance. *Agrobacterium*-mediated transformation of plant nuclei is accomplished according to the following procedure:

- (1) the gene is inserted into the selected *Agrobacterium* binary vector;
- (2) transformation is accomplished by co-cultivation of plant tissue (e.g., leaf discs) with a suspension of recombinant *Agrobacterium*, followed by incubation (e.g., two days) on growth medium in the absence of the drug used as the selective medium (see, e.g., Horsch et al. 1985, Cold Spring Harb Symp Quant Biol. 50:433-7);
- (3) plant tissue is then transferred onto the selective medium to identify transformed tissue; and
- (4) identified transformants are regenerated

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to intact plants.

It should be recognized that the amount of expression, as well as the tissue specificity of expression of the *plPAC* gene in transformed plants can vary depending on the position of their insertion into the nuclear genome. Such position effects are well known in the art. For this reason, several nuclear transformants should be regenerated and tested for expression of the transgene.

10

IV. Uses of *PlPAC* Nucleic Acids, Encoded Proteins and Antibodies

1. *PlPAC* Nucleic Acids

15

PlPAC nucleic acids may be used for a variety of purposes in accordance with the present invention. The DNA, RNA, or fragments thereof may be used as probes to detect the presence of and/or expression of *plPAC* genes. Methods in which *plPAC* nucleic acids may be utilized as probes for such assays include, but are not limited to: (1) *in situ* hybridization; (2) Southern hybridization (3) northern hybridization; and (4) assorted amplification reactions such as polymerase chain reactions (PCR).

20

25

The *plPAC* nucleic acids of the invention may also be utilized as probes to identify related genes from other plant species. As is well known in the art and described above, hybridization stringencies may be adjusted to allow hybridization of nucleic acid probes with complementary sequences of varying degrees of homology. Thus, *plPAC* nucleic acids may be used to advantage to identify and characterize other genes of varying degrees of relation to the exemplary *ATPAC*, thereby enabling further characterization of this family

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of genes in plants. Additionally, they may be used to identify genes encoding proteins that interact with the P-glycoprotein encoded by *plPAC* (e.g., by the "interaction trap" technique).

5

2. *PlPAC* Proteins and Antibodies

Purified *plPAC*-encoded P-glycoproteins, or fragments thereof, may be used to produce polyclonal or monoclonal antibodies which also may serve as sensitive
10 detection reagents for the presence and accumulation of plant P-glycoproteins in cultured plant cells or tissues and in intact plants. Recombinant techniques enable expression of fusion proteins containing part or all of the *plPAC*-encoded protein. The full length protein or
15 fragments of the protein may be used to advantage to generate an array of monoclonal or polyclonal antibodies specific for various epitopes of the protein, thereby providing even greater sensitivity for detection of the protein in cells or tissue.

20 Polyclonal or monoclonal antibodies immunologically specific for *plPAC*-encoded proteins may be used in a variety of assays designed to detect and quantitate the protein. Such assays include, but are not limited to: (1) flow cytometric analysis; (2)
25 immunochemical localization in cultured cells or tissues; and (3) immunoblot analysis (e.g., dot blot, Western blot) of extracts from various cells and tissues.

Polyclonal or monoclonal antibodies that immunospecifically interact with one or more of the
30 polypeptides encoded by *plPAC* can be utilized for identifying and purifying such proteins. For example, antibodies may be utilized for affinity separation of proteins with which they immunospecifically interact. Antibodies may also be used to immunoprecipitate proteins

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from a sample containing a mixture of proteins and other biological molecules.

3. plPAC Transgenic Plants

5 Transgenic plants that over- or under- express plPAC can be used in a varied of agronomic and research applications. From the foregoing discussion, it can be seen that plPAC and its homologs, and transgenic plants containing them will be useful for improving stress
10 resistance or tolerance in plants. This provides an avenue for developing marginal or toxic soil environments for crop production. Both over- and under-expressing plPAC transgenic plants have great utility in the research of herbicides and other xenobiotic compounds.

15 As discussed above and in greater detail in Example 1, the similarity between plant and mammalian *mdr* genes indicates that their functional aspects will also be conserved. Thus, plPAC is expected to play an important role in the exclusion of toxic metabolic or
20 xenobiotic compounds from cells. The fact that plPAC also is inducible and appears to be preferentially expressed in roots, where contact with such compounds often occurs, makes plPAC particularly desirable for genetic engineering of plants to increase their tolerance
25 to such compounds. Accordingly, plants engineered to overexpress the plPAC gene should be resistant to a wide range of chemicals, both intentionally applied as herbicides or unintentionally as wastes. Examples of the kinds of xenobiotics that should be detoxified by the
30 plPAC of the invention include, but are not limited to, hydrophobic (i.e., lipophilic) herbicides and other compounds, such as 3(3,4-dichlorophenyl)-1,1, dimethyl urea (also known as DCMU or Diuron, available from Sigma Chemical Co., St. Louis, MO) or other hydrophobic

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compounds that disrupt photosynthetic electron transport, as well as Metachlor (Ciba Geigy, Basel Switzerland), Taurocholate (Sigma Chemical Co.), Primisulfuron (Ciba Geigy), and IRL-1803.

5 As illustrated in Example 2, plant cells that over-express a *plPAC* gene have surprisingly higher growth rate with or without the xenobiotic compound Rhodamine 6G. It is contemplated that *plPAC* overexpression may be a generally useful way to increase plant and plant cell
10 culture growth, even without the presence of xenobiotic compounds.

The following specific examples are provided to illustrate embodiments of the invention. They are not
15 intended to limit the scope of the invention in any way.

EXAMPLE 1

20 Cloning and Analysis of a *plPAC* From *Arabidopsis thaliana*

The *plPAC* of the present invention was identified by its up-regulation in response to a chloride
25 ion channel blocker. *Brassica napus* plants were grown either in the presence or absence of 20 μ M 5-nitro-2-(3-phenylpropylamino) benzoic acid (NPPB). After five days, the roots of the seedlings were harvested and total RNA was extracted separately from the treated and untreated
30 plants. From the total RNA preparations, poly (A)+ RNA was isolated and used as the starting material to create a cDNA subtraction library, using the CLONTECH PCR-SELECT™ cDNA Subtraction Kit and accompanying instructions (CLONTECH Laboratories, Inc., Palo Alto,
35 CA).

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Using the subtractive hybridization kit, a gene fragment was identified that was up-regulated in response to treatment of the plants with NPPB. This fragment (0.5 kb) was used to screen a cDNA library of *Arabidopsis thaliana*, from which a full-length cDNA clone was isolated. The nucleotide sequence of this cDNA clone, referred to as ATPAC (*Arabidopsis thaliana* putative anion channel) is set forth below as SEQ ID NO:1.

The 3.76 kb cDNA clone encodes a polypeptide 1,254 amino acids in length. The deduced amino acid sequence encoded by SEQ ID NO:1 is shown in Figure 1 as "atpac" (SEQ ID NO:2), in a lineup with the following sequences: (1) hmdr1 (SEQ ID NO:3); (2) mmdr1 (SEQ ID NO:4); (3) hmdr3 (SEQ ID NO:5); (4) mmdr2 (SEQ ID NO:6); (5) atpgp1 (SEQ ID NO:7); and (6) atpgp2 (SEQ ID NO:8). A consensus sequence (SEQ ID NO:9) is also shown.

A search of various sequence databases indicates that ATPAC is a new and distinct member of the *mdr* family of ABC transporters. In none of the databases, including the EST collection, does an exact match exist. The ABC transporter family is very large, consisting of at least two sub-groups, *mrp* and homologs and *mdr* and homologs. The only examples of plant *mdr*-like genes are *atpgp1* and *atpgp2* from *A. thaliana* and two homologs from potato and barley, respectively. Though the *atpgp1* and *atpgp2* genes are similar to ATPAC, they are only 51 and 50% identical, respectively, indicating that ATPAC is a distinct gene by comparison. Sequence homology with the potato and barley *mdr*-like genes is even more divergent. Another difference between the *atpgp1* gene and the ATPAC gene is their respective preferential expression in inflorescens and roots, respectively.

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EXAMPLE 2

Effect of ATPAC Expression in Bacterial Cells
on Their Ability to Detoxify Rhodamine 6G

5 The compound Rhodamine 6G is a well known
substrate of mammalian p-glycoproteins (Kolaczowski et
al., J. Biol. Chem. 271: 31543-31548, 1996). The ability
10 of a cell to detoxify the compound is indicative of
activity of p-glycoproteins. A bacterial cell line was
transformed with an expression vector comprising ATPAC.
The growth rate of transformed and non-transformed cells
was then measured, in the presence or absence of
15 Rhodamine 6G. Results are shown in Figure 2. As can be
seen, ATPAC-expressing cells grown in the absence of the
drug had the best growth rate. Moreover, even in the
presence of the drug, the cells grew more quickly than
non-transformed cells in the presence or absence of
20 Rhodamine 6G. These results demonstrate that ATPAC
encodes a functional and robust p-glycoprotein.

Example 3

Transgenic Plants the Overexpress
and Underexpress ATPAC

25 Transformation construct. The *Agrobacterium*
binary vector pPZP211 (Hajdukiewicz et al., 1994 Plant
Mol. Biol. 25:989-994) was digested with *EcoRI* and *SmaI*,
30 and self-ligated. This molecule was named pPZP211'. The
Agrobacterium binary vector pCGN7366 (Calgene, CA) was
digested with *XhoI* and cloned in *SalI*-digested pPZP211'.
We named this binary vector pPZP-PCGN. The 3.8 kb full-
length ATPAC cDNA was cloned into the pGH19 vector.
35 After digestion with *SmaI* (in the multiple cloning site
upstream) and *EcoRI*, a 3.1 kb cDNA fragment was cut out.

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This *SmaI-EcoRI* 3.1 kb fragment was cloned into the *SmaI/EcoRI* site of pPZP-pCGN. The rest of *ATPAC* gene was amplified using polymerase chain reaction to have translationally fused HA-tag at its 3'-terminal. After
5 ligating *EcoRI* linkers to the ends of the resulting PCR product, the 0.7 kb fragment was cloned into the *EcoRI* site of the *SmaI-EcoRI* 3.1 kb *ATPAC* fragment in pPZP-pCGN. The final construct was named pATPAC-OE.

Plant transformation. pATPAC-OE was introduced
10 into *Agrobacterium tumefaciens* strain by a direct transformation method. *Agrobacterium*-mediated transformation was performed using vacuum infiltration (Bechtold et al., 1993, . CR Acad. Sci. [III] 316: 1194-1199.)

15 T1 plants which survived on kanamycin-containing plates were selected, transplanted into soil and grown to set T2 seed. T3 seeds were collected from kanamycin-resistant T2 plants. T3 plants which showed 100% kanamycin-resistance were selected and
20 were considered homozygous for the transgene.

Antisense Plants. The full length cDNA in pBluescript SK(-) vector (Stratagene, CA) is digested with *EcoRI* (there is a cleavage site in the upstream
25 polylinker) and *SspI*. The resulting 1.3 Kb fragment representing a 5' portion of the *AtPAC* cDNA was cloned into the aforementioned pPZP-PCGN, which had been digested with *EcoRI/SmaI*, ensuring that this fragment of the cDNA was inserted in the antisense orientation. This
30 construct was named pATPAC-AE. pATPAC-AE was introduced into *Arabidopsis* plants by *Agrobacterium* transformation, as described above.

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Knock-out Plants. The method of Krysan et al (1996, PNAS 93:8145, incorporated by reference herein) was followed using the following primers:

Gene-specific primers:

5 AtpacF: CACTGCTCAATGATCTCGTTTTCTCACTA (SEQ ID NO:11)

AtpacR: CTTGAATCACACCAATGCAATCAACACCTC (SEQ ID NO:12)

Primers for T-DNA left boarder:

JL202: CATTTTATAATAACGCTGCGGACATCTAC (SEQ ID NO:13)

JL270: TTTCTCCATATTGACCATCATACTCATTG (SEQ ID NO:14)

10

While certain of the preferred embodiments of the present invention have been described and specifically exemplified above, it is not intended that the invention be limited to such embodiments. Various
15 modifications may be made thereto without departing from the scope and spirit of the present invention, as set forth in the following claims.

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What is claimed:

1. A nucleic acid isolated from a plant, which encodes a p-glycoprotein that is inducible by exposure of the plant to NPPB.

2. The isolated nucleic acid of claim 1, which is preferentially expressed in plant roots upon exposure of the plant to NPPB.

3. The isolated nucleic acid of claim 1, wherein the plant is selected from the group consisting of *Brassica napus* and *Arabidopsis thaliana* and is 3850-4150 nucleotides long.

4. The isolated nucleic acid of claim 1, which has the restriction sites shown in Figure 4 for at least three enzymes.

5. The isolated nucleic acid of claim 4, which encodes a polypeptide having SEQ ID NO:2.

6. The isolated nucleic acid of claim 5, which is a cDNA comprising a coding region selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:10.

7. An isolated protein, which is a product of expression of part or all of the isolated nucleic acid molecule of claim 1.

8. Antibodies immunologically specific for the protein of claim 7.

9. A expression cassette, which comprises a

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plPAC gene coding sequence operably linked to a promoter.

10. The expression cassette of claim 9, which comprises a *plPAC* gene from *Arabidopsis thaliana*.

5

11. The expression cassette of claim 10, in which the promoter is the cauliflower mosaic virus 35S promoter.

10

12. The expression cassette of claim 10, in which the *plPAC* gene is part or all of SEQ ID NO:1 or SEQ ID NO:10.

15

13. A vector comprising the expression cassette of claim 9.

20

14. The vector of claim 13, which is comprised of an *Agrobacterium* binary vector selected from the group consisting of pPZP211 and pCGN7366.

25

15. A method for producing a plant with enhanced resistance to xenobiotic compounds by transforming *in vitro* the plant with the expression cassette of claim 9.

30

16. The method of claim 15, wherein the transformation step further uses the vector of claim 13.

17. A transgenic plant produced by the method of claim 15.

18. A reproductive unit from the transgenic plant of claim 17.

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19. A cell from the transgenic plant of claim
17.

20. A recombinant DNA molecule comprising the
5 nucleic acid molecule of claim 1, operably linked to a
vector for transforming cells.

21. A cell transformed with the recombinant
DNA molecule of claim 20.

10

22. The cell of claim 21, selected from the
group consisting of bacterial cells, yeast cells and
plant cells.

15

23. A transgenic plant regenerated from the
transformed cell of claim 22.

24. An isolated nucleic acid molecule of at
least 20 nucleotides in length having a sequence selected
20 from the group consisting of:

- a) SEQ ID NO:1 and SEQ ID NO:10;
- b) a nucleic acid sequence that is at least
about 60% homologous to the coding regions of SEQ ID NO:1
or SEQ ID NO:10;
- 25 c) a sequence hybridizing with SEQ ID NO:1 or
SEQ ID NO:10 at moderate stringency;
- d) a sequence encoding part or all of a
polypeptide having SEQ ID NO:2;
- e) a sequence encoding an amino acid sequence
30 that is at least about 70% identical to SEQ ID NO:2;
- f) a sequence encoding an amino acid sequence
that is at least about 80% similar to SEQ ID NO:2;
- g) a sequence encoding an amino acid sequence
that is at least about 40% similar to residues 1-76, 613-

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669 or 1144-1161 of SEQ ID NO:2; and

h) a sequence hybridizing at moderate stringency to a sequence encoding residues 1-76, 613-669 or 1144-1161 of SEQ ID NO:2.

5

25. A polypeptide produced by expression of the nucleic acid sequence of claim 24.

26. Antibodies immunologically specific for the polypeptide of claim 24.

27. An oligonucleotide between about 10 and about 100 nucleotides in length, which specifically hybridizes at moderate stringency with a portion of the nucleic acid molecule of claim 24.

15

28. A recombinant DNA molecule comprising the nucleic acid molecule of claim 24, operably linked to a vector for transforming cells.

20

29. A cell transformed with the recombinant DNA molecule of claim 28.

30. The cell of claim 29, selected from the group consisting of bacterial cells, yeast cells and plant cells.

25

31. A transgenic plant regenerated from the cell of claim 30.

30

32. An isolated plant p-glycoprotein, which is inducible upon exposure of the plant to NPPB.

33. The p-glycoprotein of claim 32, which

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confers upon a cell in which it is found resistance to Rhodamine 6G.

34. The p-glycoprotein of claim 33, which is
5 preferentially produced in roots upon the exposure to the NPPB.

35. The p-glycoprotein of claim 34, from a
plant selected from the group consisting of *Brassica napus*
10 and *Arabidopsis thaliana*.

36. The p-glycoprotein of claim 35, having an amino acid sequence that selected from the group consisting of:

15 a) an amino acid sequence that is at least 80% similar to SEQ ID NO:2;

b) an amino acid sequence that is at least 70% identical to SEQ ID NO:2;

c) an amino acid sequence that is at least 40%
20 similar to residues 1-76, 613-669 or 1144-1161 of SEQ ID NO:2; and

d) an amino acid sequence encoded by a nucleic acid sequence hybridizing at moderate stringency to a amino acid sequence encoding residues 1-76, 613-669 or
25 1144-1161 of SEQ ID NO:2.

37. Antibodies immunologically specific for the p-glycoprotein of claim 32.

38 The antibodies of claim 35, that are
immunologically specific to residues 1-76, 613-669 or
1144-1161 of SEQ ID NO:2.

39. A plant p-glycoprotein gene promoter which

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is inducible by NPPB.

40. The plant p-glycoprotein gene promoter of
claim 39, that is part or all of residues 1-3429 of SEQ ID
5 NO:10.

41. A plant with reduced levels of *plPAC*
protein.

10 42. The plant of claim 41, wherein the native
plPAC gene is mutated.

43. The plant of claim 42, wherein the *plPAC*
gene is mutated due to the insertion of a T-DNA.
15

44. A method for making the plant of claim 42,
wherein a population of mutated plants are screened using
at least one of SEQ ID NOS:11-14 as PCR primers.

20 45. The method of claim 44, wherein the
population of plants is mutated by T-DNA insertion.

1 MDLEGRNGGAKKNF....FKLNKSEKKKEKPT...VSFMSFRYSNWLDKLYVMVGTLLAAIIHGAGLPLMLVFGEMTDIFANAGNLEDLMSNITNRSNDINDTGFF
1 ~~~~~MSEINTTDAKTVPAEAEKKKEQSLPFFKLFSFADKFDYLLMEFVGSGLGAIIVHGSNMPVFFLLFGQMVNGFGKNQMDL.....s
1 md e g a l s dr kkk vgv lFryadw Dkl M lGtlaaiHGs lPlmmivFgemtd fa

105 MN..LEEDMTRYAYYSIGAGVLVAAIYQVSWFCLAAQPIHKIRKQFFHAIMRQEIWGFVDH.DVGELNTRLTDDVSKINEVIGDKIGMFFQSMATFFTGFIVGFTRG
102 SNSSLEEMAIYAYYTIGAGVLIVAYIQVSLWCLAAQPIHKIRKQFFHAIMRQEIWGFVDH.DVGELNTRLTDDVSKINDIGDKIGMFFQSIITFLAGFIIGFISG
77 ..HQMVEHSRYSLYFVGLVCFSSVAYEIAICWMSGERQVAALKKYLEAVIKQDVFFDDTARTGDIVFSVSTDFLLVQDAISEKVGNFHYLSFTFLAGLVGVFVSA
80 ..EKMEEVLYKALYFLVGAIAIWSWAEISCMWSGEROTTKRIKYLEAALNQDIOFFDTEVRTSDVFAINTDAVMQVDAISEKLGFIHYMATFVSGFIVGFTAV
73 ..KQASHRVAKYSLDFVYLSVAILFSSWLEVACWMTGERQAAMRRAYLRSMLODISLFDTEASTGEVISAITSIDILVVQDALSEKVGNFHYLSRFIAGFAIGFTSV
111 k leecentrYayyygslgagvlv ayiqvs W laagRQirkir kfhallrQeigwFdi tgelntrlttdiskindgigdkVgmffq vatflagfiVGfi g
consensus

214 WKLTIVIMAIPIILGLSAVWAKILSAFSDKELAAAYAKAGAAVEEALGAIRTVIAFGQNKELERYQKHLENAKEIGIKKAI SANISMGIAFLLIYASALAFWYGSTLV
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212 WKLTIVILAIPIILGLSAVWAKILSFTDKELLAYAKAGAAVEEALGAIRTVIAFGQNKELERYQKHLENAKEIGIKKAI SANISMGIAFLLIYASALAFWYGSTLV
211 WKLTIVILAIPIILGLSALWAKILSFTDNKELQAYAKAGAAVEEALGAIRTVIAFGQNKELERYQKHLENAKEIGIKKAI SANISMGIAFLLIYASALAFWYGSTLV
185 WKALLSVAVIPGIAFAGGLYATLTGITSRESYANAGVIAEQAIQVTVYSYVGESKALNAYSDAIQYTLKLYKAGMAKGLGCTYGIACMSWALVFWYAGVFI
188 WQIALVTLAVVPLIAVIGGIHTTTLTKLSNKSQESLSQAGNIVEQTVVQIRVMAFVGESRASQAYSSALKIAQKLYTKGLAKGMGLGATYFVFCYALLLWYGGYLV
181 WQISLVTLIVPLIALAGGIYAFVAILIARVRSYIKAGEIAEEVIGNVTVQAFTEGEERAVRLYREALENTKYGRKAGLTGKLGSGMHCVLFLSWALLVWFTSWV
221 WkltlvilaisPiiglsaaavwakils fs kel ayakagavaEe lGaiRtViafgGq kelerYqk le akkiGiKkaisa ismG afliliyasYAlafWygstlv
consensus

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321 LSKEYSIGEVLTFFSILIGAFSVGQAAPSIDAFANARGAAVEIFKIIDNKPSIDSYSKSGHKPDNIKNLEFRNVHFSYPSRKEVKILKGLNLKVQSGQTVALVGS
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298 RHHLTNGGLATMFAVMIGGLALGQAPSPMAAFKAKVAAAKTFRIIDHKPTIERNSESGVELDSTGIVELKNVDVFSYPSRDPDMIVKILNNFCLISVPAGKTIALVGS
291 HKDIADGGKSTTMLNVVIALGSLGQAAPDISAFVRAKAAAYPIFKMIERTVTKTSAKSGRKLGVGHQIFKQDATFSYPSRDPDMIVFDRLNLAIIPAGKIVALVGS
331 is eytiG amtvffsiligafsvGqaap idAFanargAay ifkildn psidsfs Ghkpd ikgnlefkdvHfsYpSR evkilkgnlv sgqtvalVG sGc
consensus

Figure 1 (sheet 1 of 4)

hmdr3 434 GKSTTVQLIQRLYDPDEGTINIDGDIRNFNVNRYLREIIGVSOBPLVFSTTIAENICYGRGNVTMDIEIKAVKEANAYEFIMKLPQKEDTLVGERGAQLSGGQKQRIAI
hmdr2 431 GKSTTVQOLLQRLYDPTGKISIDGQDIRNFNVNRYLREIIGVSOBPLVFSTTIAENICYGRGNVTMDIEIKAVKEANAYEFIMKLPQKEDTLVGERGAQLSGGQKQRIAI
hmdr1 432 GKSTTVQOLMQLYDPTGKISIDGQDIRNFNVNRYLREIIGVSOBPLVFSTTIAENICYGRGNVTMDIEIKAVKEANAYEFIMKLPQKEDTLVGERGAQLSGGQKQRIAI
hmdr1 431 GKSTTVQOLMQLYDPTGKISIDGQDIRNFNVNRYLREIIGVSOBPLVFSTTIAENICYGRGNVTMDIEIKAVKEANAYEFIMKLPQKEDTLVGERGAQLSGGQKQRIAI
atpac 405 GKSTTVSLIERFVDPNSGQILLDGVBEIKTLQKFLREQILGNQBPALFATILENLYGKPDATMVEEAAAANAHAHSFIILLPKGYDTQVGERGVQLSGGQKQRIAI
atpgp1 408 GKSTTVSLIERFVDPNSGQILLDGVBEIKTLQKFLREQILGNQBPALFATILENLYGKPDATMVEEAAAANAHAHSFIILLPKGYDTQVGERGVQLSGGQKQRIAI
atpgp2 401 GKSTTVSLIERFVDPNSGQILLDGVBEIKTLQKFLREQILGNQBPALFATILENLYGKPDATMVEEAAAANAHAHSFIILLPKGYDTQVGERGVQLSGGQKQRIAI
consensus 441 GKSTTVQLIQRLYDPTGKISIDGQDIRNFNVNRYLREIIGVSOBPLVFSTTIAENICYGRGNVTMDIEIKAVKEANAYEFIMKLPQKEDTLVGERGAQLSGGQKQRIAI

W_B

hmdr3 544 ARALVRNPKILLDEATSALDTESEAEVQOALDKAREGRITIVIAHRLSTVRNADVIAGFEDGVIVEQGHSELMKK..EGVYFKLVNMOTSGSQIOSEE.....F.
hmdr2 541 ARALVRNPKILLDEATSALDTESEAEVQOALDKAREGRITIVIAHRLSTVRNADVIAGFEDGVIVEQGHSELMKK..EGYFRLVNMOTAGSQILSEE.....FE
hmdr1 542 ARALVRNPKILLDEATSALDTESEAEVQOALDKAREGRITIVIAHRLSTVRNADVIAGFEDGVIVEQGHSELMKK..KGIYFKLVMTQTAGNEVELEEN.....AA
hmdr1 541 ARALVRNPKILLDEATSALDTESEAEVQOALDKAREGRITIVIAHRLSTVRNADVIAGFEDGVIVEQGHSELMKK..KGIYFKLVMTQTRGNEIEFEN.....NA
atpac 515 ARALVRNPKILLDEATSALDTESEAEVQOALDKAREGRITIVIAHRLSTVRNADVIAGFEDGVIVEQGHSELMKK..SGAYASLIRFQEMVGTDRDFSNPSTRSTRSTR
atpgp1 518 ARALVRNPKILLDEATSALDTESEAEVQOALDKAREGRITIVIAHRLSTVRNADVIAGFEDGVIVEQGHSELMKK..NPDGAYSLIRLQETASLQRPNSLNRILSRPHS
atpgp2 511 SRAIVKNPSILLDEATSALDTESEAEVQOALDKAREGRITIVIAHRLSTVRNADVIAGFEDGVIVEQGHSELMKK..GVYFKLVMTQTAGNEVELEEN.....AA
consensus 551 ARALVRNPKILLDEATSALDTESEAEVQOALDKAREGRITIVIAHRLSTVRNADVIAGFEDGVIVEQGHSELMKK..GVYFKLVMTQTAGNEVELEEN.....AA

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hmdr1 641 YGQSDTDASELTSEESKSPILR.SRIYRSVHRKQDQE...RRLSKAEAVDEDPVLSFWRILNLSNLPSEWYFVGTVCALANGLOQPAFSPVFSEIIFGPGDD..AVK
atpac 623 LSHSLSTKSLSL...RSGSLRNLSSYSTGADGRIEMISNAETDRKTRA...PENYFVRLKLSNLPSEWYFVGTVCALANGLOQPAFSPVFSEIIFGPGDD..AVK
atpgp1 628 ARNSVSSPIMTRNSSYGRSPYRRLSDFTSDFSIDSASSYPNRYRNEKLAQDQANSFWRILKMSPEWYFVGTVCALANGLOQPAFSPVFSEIIFGPGDD..AVK
atpgp2 620 IKYS.....RELSTRSSFCSESR.ESVTRPDGADPSKVKVTVG...RLYSMIRPDWYGVGTICAFIAGSOMPLFALGVSOAL.VSYSGWDETDQ
consensus 661 s e a m ks l R s s qd r d le vp vsfwrvlkln teWpY vvgTvcailing lqp Failis iiaVf dd vk

hmdr3 748 QQKNMFSILFLGLISFFFTFLOGFTFGKAGEIILTRRLRSNAFKAMLRQDMSWFDDHKNSTGALSTRLATDAAQVQCATGTRLALIAQNIANLGTGIIISFIYGWOLT
hmdr2 745 QQKNMFSILFLGLISFFFTFLOGFTFGKAGEIILTRRLRSNAFKAMLRQDMSWFDDHKNSTGALSTRLATDAAQVQCATGTRLALIAQNIANLGTGIIISFIYGWOLT
hmdr1 749 RONSNLFSILFLGLISFFFTFLOGFTFGKAGEIILTRRLRSNAFKAMLRQDMSWFDDHKNSTGALSTRLATDAAQVQCATGTRLALIAQNIANLGTGIIISFIYGWOLT
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atpgp1 725 RK.TKEYVFIYIGAGLVAGAYLTIQHYFSGIMGENTLTVRRRMMLSAIILNEVGFDEDEHNSLIAARLADADVKSAIABRISVILQNMVTSLSFIVAFIVEWTRVS
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consensus 707 KE.IKKIAILFCCASVITLIVYIEHICFGFMGERLTLVRNENMFRAILKNEIGWFDEVDNTSSMLASRIESDAILTKTIVVDRSTILLQNLGLVTSFIILNWRULT
771 rq nifsliflglgilsfiflqgftfgkageiilTrKvR mvfkamLrqdmSWFDD knstg lstrLatDaaqVkgaiG rlaVi QNianlgtgiiisfiyGwqlt

Figure 1 (sheet 2 of 4)

hmdr3 858 LLLAVVPIIAVSGIVEMKLLAGNAKRDKELEAAGKIAIEAENIRTVWSTQERKFESMYVEKLYGPNRSV..OKAHYIGITFSISOAFMYFSYAGCFRFGAYLIVN
hmdr2 855 LLLSVVPIIAVAGIVEMKLLAGNAKRDKELEAAGKIAIEAENIRTVWSTQERKFESMYVEKLYGPNRSV..RKAHYIGITFSISOAFMYFSYAGCFRFGAYLIVN
hmdr1 859 LLLAIVPIIAIAGVEMKLLSQAALDKKKELEGAGKIAIEAENIRTVWSTQERKFESMYVEKLYGPNRSV..RKAHYIGITFSISOAFMYFSYAGCFRFGAYLIVN
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atpac 834 LILGTFTPIIVLANFAAQAQSLKGFAGDPAKAKHAKTSMIAGGVSNI RTVAFAAQAQSLKGFAGDPAKAKHAKTSMIAGGVSNI RTVAFAAQAQSLKGFAGDPAKAKHAKTSMIAGGVSNI
atpgp1 847 LVLVATFPVVVAATVLOKMFMTGFGDLEAAHAKTQLAGAIAINRTVAFAAQAQSLKGFAGDPAKAKHAKTSMIAGGVSNI RTVAFAAQAQSLKGFAGDPAKAKHAKTSMIAGGVSNI
atpgp2 816 LVLVATFPVVVAATVLOKMFMTGFGDLEAAHAKTQLAGAIAINRTVAFAAQAQSLKGFAGDPAKAKHAKTSMIAGGVSNI RTVAFAAQAQSLKGFAGDPAKAKHAKTSMIAGGVSNI
consensus 881 Llllavvpiivvavivemkll Gna rdkk le agkiaEaieNirvvslt e Kfesmy L Pynsv rkahiyGittfsisQa myfsyagcfrfgaylv h

W_A

hmdr3 966 GHRFRDVIIVFSAIVFGAVALGHASSFAPDYAKAKLSAAHLMFLFEROPLIDSYSSEGL.KPDKFEGNITFNEWVFNYPTRANVPVLQGLSLEVKKGQTIALVGSsGCG
hmdr2 963 GHRFRDVIIVFSAIVFGAVALGHASSFAPDYAKAKLSAAHLMFLFEROPLIDSYSSEGL.WPDKFEGSVTFNEWVFNYPTRANVPVLQGLSLEVKKGQTIALVGSsGCG
hmdr1 967 KLSFEDVLLVFSVAVFGAMAVGVSSFAPDYAKAKLSAAHLMFLFEROPLIDSYSSEGL.MPTLEGNVTFEGVFNYPTRANVPVLQGLSLEVKKGQTIALVGSsGCG
hmdr1 965 QMTFENVMLVFSVAVFGAMAGNTSSFAPDYAKAKLSAAHLMFLFEROPLIDSYSSEGL.KPTLLEGNVTFEGVFNYPTRANVPVLQGLSLEVKKGQTIALVGSsGCG
atpac 944 GVTFskVIVFVVLVITANSVAETVSLAPEIIRGGEAVGSVSVLDRQTRIDPDADADPV.ETIRGDIIEFRHVDFAFESRPDMVFRDFNLIRAGHSQAALVGSsGCG
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atpgp2 924 GLAGFKSVMTFMVLIIVTALAMGETLALAPDLLKGNQMVASVFEILLDRKTQIV...GETSEELNNVEGTIELKGVHFSYSPRPDMVFRDFNLIRAGHSQAALVGPSSGCG
consensus 991 glm F vllvfsaivlgAvalg tssfApyakaklsaa lf hier p Idsys egl pd leg v f v FnyPrpdpvplqglsllevkkgqtialVGSsGCG

hmdr3 1075 KSTVVQLLERFYDPLAGVILLDGOEAKKLVQWLRQAQIGVSOEPILFDCSIAENIAYGDNRSRVSOEIVSAAKAAHHPFIETLPHKYETRVGDKGTQLSGGQKORIA
hmdr2 1072 KSTVVQLLERFYDPMAGSVILLDGOEAKKLVQWLRQAQIGVSOEPILFDCSIAENIAYGDNRSRVSOEIVSAAKAAHHPFIETLPHKYETRVGDKGTQLSGGQKORIA
hmdr1 1076 KSTVVQLLERFYDPLAGVILLDGOEAKKLVQWLRQAQIGVSOEPILFDCSIAENIAYGDNRSRVSOEIVSAAKAAHHPFIETLPHKYETRVGDKGTQLSGGQKORIA
hmdr1 1074 KSTVVQLLERFYDPMAGSVILLDGOEAKKLVQWLRQAQIGVSOEPILFDCSIAENIAYGDNRSRVSOEIVSAAKAAHHPFIETLPHKYETRVGDKGTQLSGGQKORIA
atpac 1053 KSSVTAMIERFYDPLAGVILLDGOEAKKLVQWLRQAQIGVSOEPILFDCSIAENIAYGDNRSRVSOEIVSAAKAAHHPFIETLPHKYETRVGDKGTQLSGGQKORIA
atpgp1 1065 KSSVTSLIORFYEPPSGRMIDGKDIRKYNLKAIRKHIAIVPOBPCLFGTTIYENIAYGHEC..ATEAEIIQAATLASAHKFIETLPHKYETRVGDKGTQLSGGQKORIA
atpgp2 1031 KSSVTSLIORFYDPTAGKVMIEGKDIIKKDLKALRKHIGLVQBPALFATIIYENIAYGHEC..ASQSEVESAMLANAHSFITSLEPEGYSTKVGGERGVQMSGGQKORIA
consensus 1101 KStVvqqlleRfYdplaGkvllldGkeikklnvqwlRahligiVsQEPilFdcSiaeNiaYgdnsr vs dEiv aak Anih FietLPdky TrVGdkgtQLSGGQKORIA

Figure 1 (sheet 3 of 4)

W_B

hmdr3	1185	IARALIRQPIILLDEATSEKVVQAEALDKAREGTCIVIAHRLSTIQNADLIIVFQNGRVKEHGTHQQLLAQK..GIYFSMVSVOAGTQNL~~~~~
nmldr2	1182	IARALIRQPRVILLDEATSEKVVQAEALDKAREGTCIVIAHRLSTIQNADLIIVFQNGRVKEHGTHQQLLAQK..GIYFSMVIQAGTQNL~~~~~
hmdr1	1186	IARALVRQPHILLDEATSEKVVQAEALDKAREGTCIVIAHRLSTIQNADLIIVFQNGRVKEHGTHQQLLAQK..GIYFSMVSVOAGTKRQ~~~~~
nmldr1	1184	IARALVRQPHILLDEATSEKVVQAEALDKAREGTCIVIAHRLSTIQNADLIIVFQNGRVKEHGTHQQLLAQK..GIYFSM..VOAGAKRS~~~~~
atpac	1161	IARAVLKNPTVILLDEATSEKVVQAEALDKAREGTCIVIAHRLSTIQNADLIIVFQNGRVKEHGTHQQLLAQK..GIYFSM..VOAGAKRS~~~~~
atpgp1	1173	IARALVRKAEIILLDEATSEKVVQAEALDKAREGTCIVIAHRLSTIQNADLIIVFQNGRVKEHGTHQQLLAQK..GIYFSM..VOAGAKRS~~~~~
atpgp2	1139	IARALIRKPAIILLDEATSEKVVQAEALDKAREGTCIVIAHRLSTIQNADLIIVFQNGRVKEHGTHQQLLAQK..GIYFSM..VOAGAKRS~~~~~
consensus	1211	IARALIRGP IILLDEATSEKVVQAEALDKAREGTCIVIAHRLSTIQNADLIIVFQNGRVKEHGTHQQLLAQK..GIYFSMVSVOAGTQNL~~~~~
hmdr3	1280	~~~~~
nmldr2	1277	~~~~~
hmdr1	1281	~~~~~
nmldr1	1277	~~~~~
atpac	1255	~~~~~
atpgp1	1283	EDDA
atpgp2	1234	~~~~~
consensus	1321	

Figure 1 (sheet 4 of 4)

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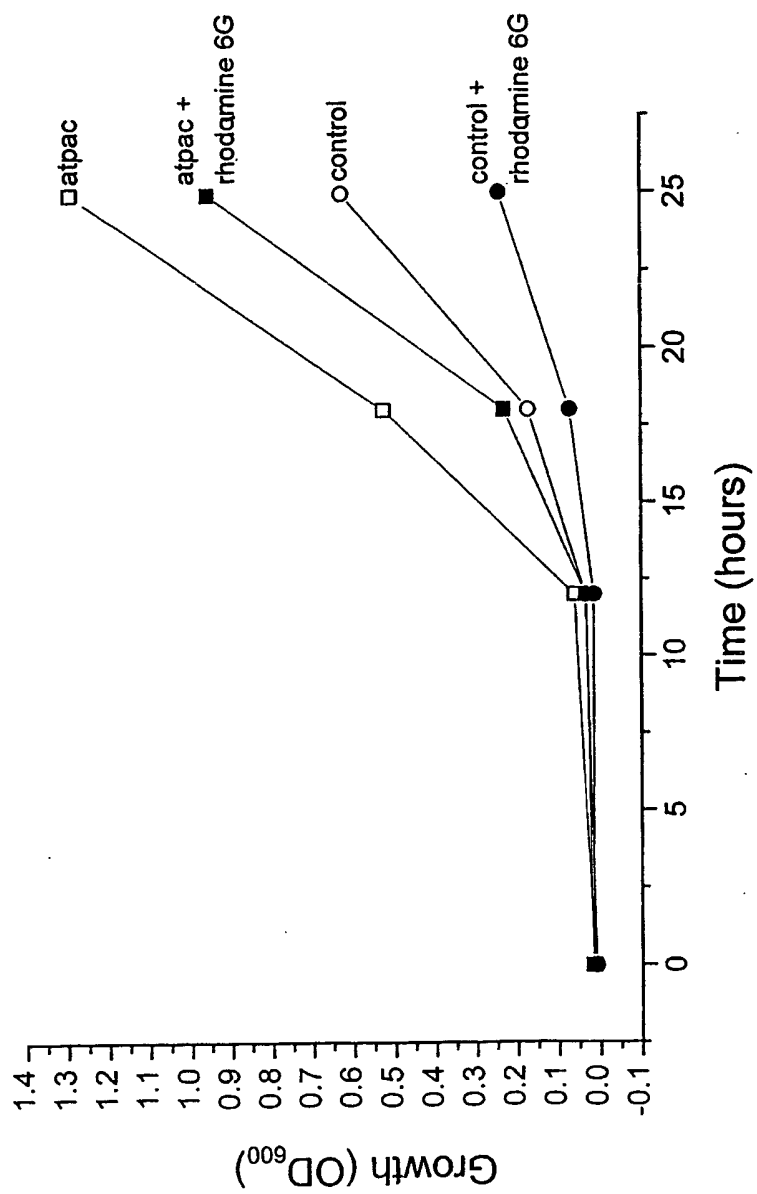


Figure 2

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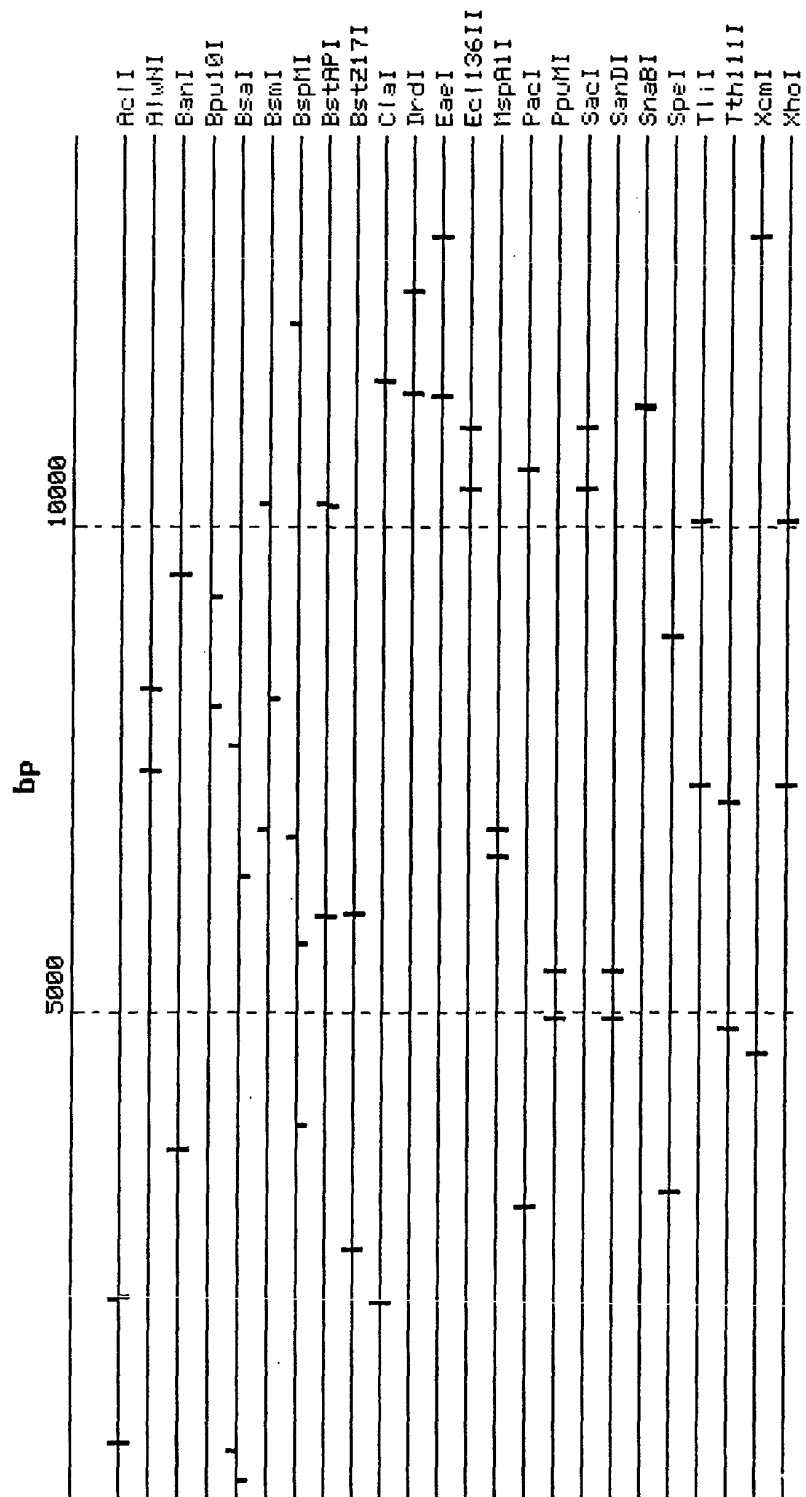


Figure 3

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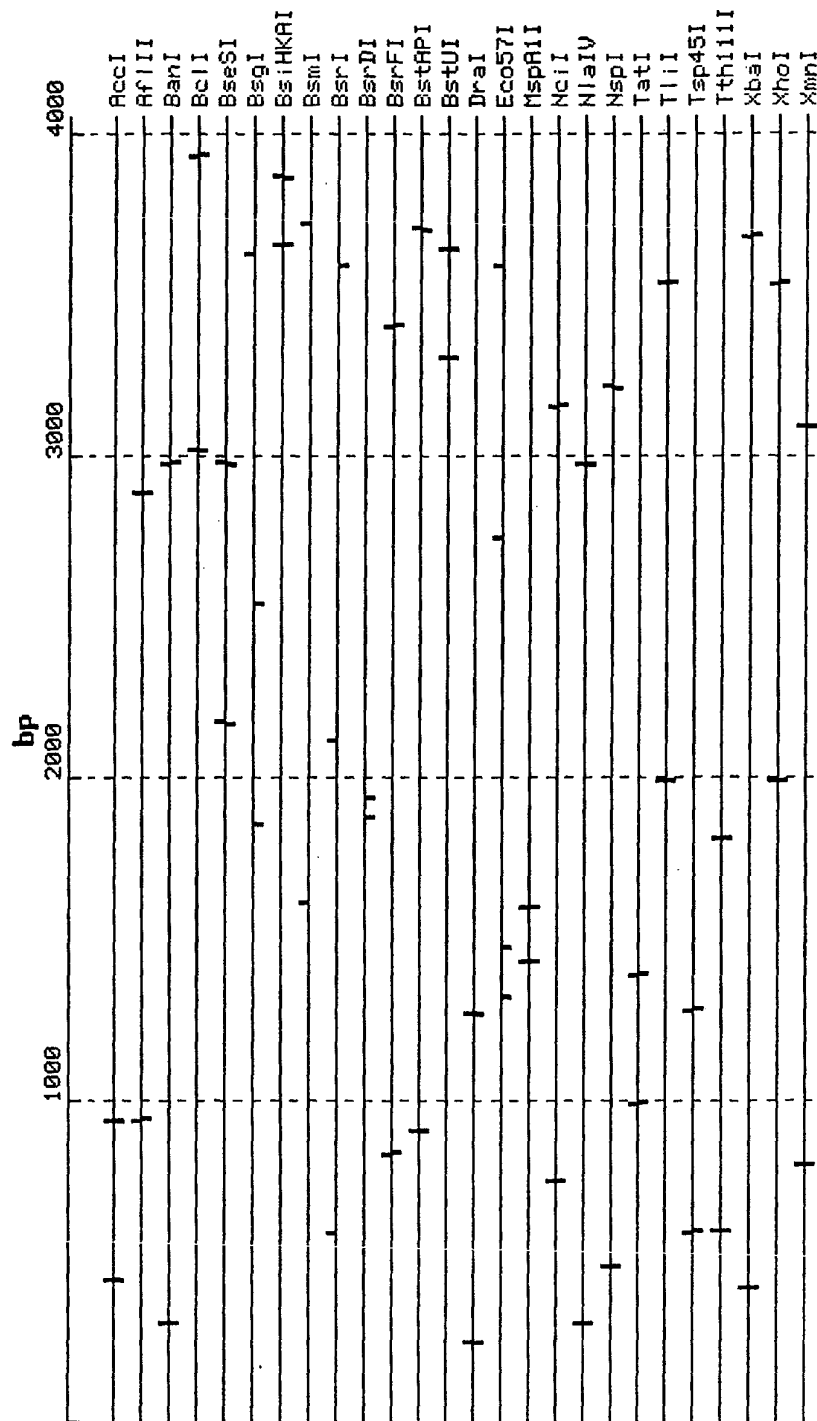


Figure 4

1.

SEQUENCE LISTING

<110> Wisconsin Alumni Research Foundation
Spalding, Edgar P.
Noh, Bosl

<120> Xenobiotic Detoxification Gene from
Plants

<130> WARF S212

<150> 60/101,814

<151> 1998-09-25

<160> 14

<170> FastSEQ for Windows Version 3.0

<210> 1

<211> 4051

<212> DNA

<213> Arabidopsis thaliana

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<221> misc feature

<222> (94)...(0)

<223> Translation start codon

<221> misc feature

<222> (3932)...(0)

<223> Stop codon

<400> 1

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2.

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cacgcttgtt ccaccataag aggtgttgat tgcattggtg tgattcaaga cgggcggatt 3840
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<211> 1254

<212> PRT

<213> Arabidopsis thaliana

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      20           25           30
Ala Asp Lys Phe Asp Tyr Leu Leu Met Phe Val Gly Ser Leu Gly Ala
      35           40           45
Ile Val His Gly Ser Ser Met Pro Val Phe Phe Leu Leu Phe Gly Gln
      50           55           60
Met Val Asn Gly Phe Gly Lys Asn Gln Met Asp Leu His Gln Met Val
      65           70           75           80
His Glu Val Ser Arg Tyr Ser Leu Tyr Phe Val Tyr Leu Gly Leu Val
      85           90           95
Val Cys Phe Ser Ser Tyr Ala Glu Ile Ala Cys Trp Met Tyr Ser Gly
      100          105          110
Glu Arg Gln Val Ala Ala Leu Arg Lys Lys Tyr Leu Glu Ala Val Leu

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610	615	620
His Ser Leu Ser Thr Lys Ser Leu Ser Leu Arg Ser Gly Ser Leu Arg		
625	630	635
Asn Leu Ser Tyr Ser Tyr Ser Thr Gly Ala Asp Gly Arg Ile Glu Met		640
	645	650
Ile Ser Asn Ala Glu Thr Asp Arg Lys Thr Arg Ala Pro Glu Asn Tyr		655
	660	665
Phe Tyr Arg Leu Leu Lys Leu Asn Ser Pro Glu Trp Pro Tyr Ser Ile		670
	675	680
Met Gly Ala Val Gly Ser Ile Leu Ser Gly Phe Ile Gly Pro Thr Phe		685
	690	695
Ala Ile Val Met Ser Asn Met Ile Glu Val Phe Tyr Tyr Thr Asp Tyr		700
705	710	715
Asp Ser Met Glu Arg Lys Thr Lys Glu Tyr Val Phe Ile Tyr Ile Gly		720
	725	730
Ala Gly Leu Tyr Ala Val Gly Ala Tyr Leu Ile Gln His Tyr Phe Phe		735
	740	745
Ser Ile Met Gly Glu Asn Leu Thr Thr Arg Val Arg Arg Met Met Leu		750
	755	760
Ser Ala Ile Leu Arg Asn Glu Val Gly Trp Phe Asp Glu Asp Glu His		765
	770	775
Asn Ser Ser Leu Ile Ala Ala Arg Leu Ala Thr Asp Ala Ala Asp Val		780
785	790	795
Lys Ser Ala Ile Ala Glu Arg Ile Ser Val Ile Leu Gln Asn Met Thr		800
	805	810
Ser Leu Leu Thr Ser Phe Ile Val Ala Phe Ile Val Glu Trp Arg Val		815
	820	825
Ser Leu Leu Ile Leu Gly Thr Phe Pro Leu Leu Val Leu Ala Asn Phe		830
	835	840
Ala Gln Gln Leu Ser Leu Lys Gly Phe Ala Gly Asp Thr Ala Lys Ala		845
	850	855
His Ala Lys Thr Ser Met Ile Ala Gly Glu Gly Val Ser Asn Ile Arg		860
865	870	875
Thr Val Ala Ala Phe Asn Ala Gln Ser Lys Ile Leu Ser Leu Phe Cys		880
	885	890
His Glu Leu Arg Val Pro Gln Lys Arg Ser Leu Ser Leu Tyr Arg Ser		895
	900	905
Gln Thr Ser Gly Phe Leu Phe Gly Leu Ser Gln Leu Ala Leu Tyr Gly		910
	915	920
Ser Glu Ala Leu Ile Leu Trp Tyr Gly Ala His Leu Val Ser Lys Gly		925
	930	935
Val Ser Thr Phe Ser Lys Val Ile Lys Val Phe Val Val Leu Val Ile		940
945	950	955
Thr Ala Asn Ser Val Ala Glu Thr Val Ser Leu Ala Pro Glu Ile Ile		960
	965	970
Arg Gly Gly Glu Ala Val Gly Ser Val Phe Ser Val Leu Asp Arg Gln		975
	980	985
Thr Arg Ile Asp Pro Asp Asp Ala Asp Ala Asp Pro Val Glu Thr Ile		990
	995	1000
Arg Gly Asp Ile Glu Phe Arg His Val Asp Phe Ala Tyr Pro Ser Arg		1005
	1010	1015
Pro Asp Val Met Val Phe Arg Asp Phe Asn Leu Arg Ile Arg Ala Gly		1020
1025	1030	1035
His Ser Gln Ala Leu Val Gly Ala Ser Gly Ser Gly Lys Ser Ser Val		1040
	1045	1050
Ile Ala Met Ile Glu Arg Phe Tyr Asp Leu Leu Ala Gly Lys Val Met		1055
	1060	1065
Ile Asp Gly Lys Asp Ile Arg Arg Leu Asn Leu Lys Ser Leu Arg Leu		1070
	1075	1080
Lys Ile Gly Leu Val Gln Gln Glu Pro Ala Leu Phe Ala Ala Thr Ile		1085
	1090	1095
Phe Asp Asn Ile Ala Tyr Gly Lys Asp Gly Ala Thr Glu Ser Glu Val		1100

5.

1105 1110 1115 1120
 Ile Asp Ala Ala Arg Ala Ala Asn Ala His Gly Phe Ile Ser Gly Leu
 1125 1130 1135
 Pro Glu Gly Tyr Lys Thr Pro Val Gly Glu Arg Gly Val Gln Leu Ser
 1140 1145 1150
 Gly Gly Gln Lys Gln Arg Ile Ala Ile Ala Arg Ala Val Leu Lys Asn
 1155 1160 1165
 Pro Thr Val Leu Leu Leu Asp Glu Ala Thr Ser Ala Leu Asp Ala Glu
 1170 1175 1180
 Ser Glu Cys Val Leu Gln Glu Ala Leu Glu Arg Leu Met Arg Gly Arg
 1185 1190 1195 1200
 Thr Thr Val Val Val Ala His Arg Leu Ser Thr Ile Arg Gly Val Asp
 1205 1210 1215
 Cys Ile Gly Val Ile Gln Asp Gly Arg Ile Val Glu Gln Gly Ser His
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 Ser Glu Leu Val Ser Arg Pro Glu Gly Ala Tyr Ser Arg Leu Leu Gln
 1235 1240 1245
 Leu Gln Thr His Arg Ile
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 <212> PRT
 <213> Homo sapiens

<300>
 <308> Genbank P08183
 <309> 1997-11-01

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 Thr Val Ser Val Phe Ser Met Phe Arg Tyr Ser Asn Trp Leu Asp Lys
 35 40 45
 Leu Tyr Met Val Val Gly Thr Leu Ala Ala Ile Ile His Gly Ala Gly
 50 55 60
 Leu Pro Leu Met Met Leu Val Phe Gly Glu Met Thr Asp Ile Phe Ala
 65 70 75 80
 Asn Ala Gly Asn Leu Glu Asp Leu Met Ser Asn Ile Thr Asn Arg Ser
 85 90 95
 Asp Ile Asn Asp Thr Gly Phe Phe Met Asn Leu Glu Glu Asp Met Thr
 100 105 110
 Arg Tyr Ala Tyr Tyr Tyr Ser Gly Ile Gly Ala Gly Val Leu Val Ala
 115 120 125
 Ala Tyr Ile Gln Val Ser Phe Trp Cys Leu Ala Ala Gly Arg Gln Ile
 130 135 140
 His Lys Ile Arg Lys Gln Phe Phe His Ala Ile Met Arg Gln Glu Ile
 145 150 155 160
 Gly Trp Phe Asp Val His Asp Val Gly Glu Leu Asn Thr Arg Leu Thr
 165 170 175
 Asp Asp Val Ser Lys Ile Asn Glu Val Ile Gly Asp Lys Ile Gly Met
 180 185 190
 Phe Phe Gln Ser Met Ala Thr Phe Phe Thr Gly Phe Ile Val Gly Phe
 195 200 205
 Thr Arg Gly Trp Lys Leu Thr Leu Val Ile Leu Ala Ile Ser Pro Val
 210 215 220
 Leu Gly Leu Ser Ala Ala Val Trp Ala Lys Ile Leu Ser Ser Phe Thr
 225 230 235 240
 Asp Lys Glu Leu Leu Ala Tyr Ala Lys Ala Gly Ala Val Ala Glu Glu
 245 250 255

Val	Leu	Ala	Ala	Ile	Arg	Thr	Val	Ile	Ala	Phe	Gly	Gly	Gln	Lys	Lys	260	265	270
Glu	Leu	Glu	Arg	Tyr	Asn	Lys	Asn	Leu	Glu	Glu	Ala	Lys	Arg	Ile	Gly	275	280	285
Ile	Lys	Lys	Ala	Ile	Thr	Ala	Asn	Ile	Ser	Ile	Gly	Ala	Ala	Phe	Leu	290	295	300
Leu	Ile	Tyr	Ala	Ser	Tyr	Ala	Leu	Ala	Phe	Trp	Tyr	Gly	Thr	Thr	Leu	305	310	315
Val	Leu	Ser	Gly	Glu	Tyr	Ser	Ile	Gly	Gln	Val	Leu	Thr	Val	Phe	Phe	325	330	335
Ser	Val	Leu	Ile	Gly	Ala	Phe	Ser	Val	Gly	Gln	Ala	Ser	Pro	Ser	Ile	340	345	350
Glu	Ala	Phe	Ala	Asn	Ala	Arg	Gly	Ala	Ala	Tyr	Glu	Ile	Phe	Lys	Ile	355	360	365
Ile	Asp	Asn	Lys	Pro	Ser	Ile	Asp	Ser	Tyr	Ser	Lys	Ser	Gly	His	Lys	370	375	380
Pro	Asp	Asn	Ile	Lys	Gly	Asn	Leu	Glu	Phe	Arg	Asn	Val	His	Phe	Ser	385	390	395
Tyr	Pro	Ser	Arg	Lys	Glu	Val	Lys	Ile	Leu	Lys	Gly	Leu	Asn	Leu	Lys	405	410	415
Val	Gln	Ser	Gly	Gln	Thr	Val	Ala	Leu	Val	Gly	Asn	Ser	Gly	Cys	Gly	420	425	430
Lys	Ser	Thr	Thr	Val	Gln	Leu	Met	Gln	Arg	Leu	Tyr	Asp	Pro	Thr	Glu	435	440	445
Gly	Met	Val	Ser	Val	Asp	Gly	Gln	Asp	Ile	Arg	Thr	Ile	Asn	Val	Arg	450	455	460
Phe	Leu	Arg	Glu	Ile	Ile	Gly	Val	Val	Ser	Gln	Glu	Pro	Val	Leu	Phe	465	470	475
Ala	Thr	Thr	Ile	Ala	Glu	Asn	Ile	Arg	Tyr	Gly	Arg	Glu	Asn	Val	Thr	485	490	495
Met	Asp	Glu	Ile	Glu	Lys	Ala	Val	Lys	Glu	Ala	Asn	Ala	Tyr	Asp	Phe	500	505	510
Ile	Met	Lys	Leu	Pro	His	Lys	Phe	Asp	Thr	Leu	Val	Gly	Glu	Arg	Gly	515	520	525
Ala	Gln	Leu	Ser	Gly	Gly	Gln	Lys	Gln	Arg	Ile	Ala	Ile	Ala	Arg	Ala	530	535	540
Leu	Val	Arg	Asn	Pro	Lys	Ile	Leu	Leu	Leu	Asp	Glu	Ala	Thr	Ser	Ala	545	550	555
Leu	Asp	Thr	Glu	Ser	Glu	Ala	Val	Val	Gln	Val	Ala	Leu	Asp	Lys	Ala	565	570	575
Arg	Lys	Gly	Arg	Thr	Thr	Ile	Val	Ile	Ala	His	Arg	Leu	Ser	Thr	Val	580	585	590
Arg	Asn	Ala	Asp	Val	Ile	Ala	Gly	Phe	Asp	Asp	Gly	Val	Ile	Val	Glu	595	600	605
Lys	Gly	Asn	His	Asp	Glu	Leu	Met	Lys	Glu	Lys	Gly	Ile	Tyr	Phe	Lys	610	615	620
Leu	Val	Thr	Met	Gln	Thr	Ala	Gly	Asn	Glu	Val	Glu	Leu	Glu	Asn	Ala	625	630	635
Ala	Asp	Glu	Ser	Lys	Ser	Glu	Ile	Asp	Ala	Leu	Glu	Met	Ser	Ser	Asn	645	650	655
Asp	Ser	Arg	Ser	Ser	Leu	Ile	Arg	Lys	Arg	Ser	Thr	Arg	Arg	Ser	Val	660	665	670
Arg	Gly	Ser	Gln	Ala	Gln	Asp	Arg	Lys	Leu	Ser	Thr	Lys	Glu	Ala	Leu	675	680	685
Asp	Glu	Ser	Ile	Pro	Pro	Val	Ser	Phe	Trp	Arg	Ile	Met	Lys	Leu	Asn	690	695	700
Leu	Thr	Glu	Trp	Pro	Tyr	Phe	Val	Val	Gly	Val	Phe	Cys	Ala	Ile	Ile	705	710	715
Asn	Gly	Gly	Leu	Gln	Pro	Ala	Phe	Ala	Ile	Ile	Phe	Ser	Lys	Ile	Ile	725	730	735
Gly	Val	Phe	Thr	Arg	Ile	Asp	Asp	Pro	Glu	Thr	Lys	Arg	Gln	Asn	Ser	740	745	750

7.

Asn Leu Phe Ser Leu Leu Phe Leu Ala Leu Gly Ile Ile Ser Phe Ile
 755 760 765
 Thr Phe Phe Leu Gln Gly Phe Thr Phe Gly Lys Ala Gly Glu Ile Leu
 770 775 780
 Thr Lys Arg Leu Arg Tyr Met Val Phe Arg Ser Met Leu Arg Gln Asp
 785 790 795 800
 Val Ser Trp Phe Asp Asp Pro Lys Asn Thr Thr Gly Ala Leu Thr Thr
 805 810 815
 Arg Leu Ala Asn Asp Ala Ala Gln Val Lys Gly Ala Ile Gly Ser Arg
 820 825 830
 Leu Ala Val Ile Thr Gln Asn Ile Ala Asn Leu Gly Thr Gly Ile Ile
 835 840 845
 Ile Ser Phe Ile Tyr Gly Trp Gln Leu Thr Leu Leu Leu Ala Ile
 850 855 860
 Val Pro Ile Ile Ala Ile Ala Gly Val Val Glu Met Lys Met Leu Ser
 865 870 875 880
 Gly Gln Ala Leu Lys Asp Lys Lys Glu Leu Glu Gly Ala Gly Lys Ile
 885 890 895
 Ala Thr Glu Ala Ile Glu Asn Phe Arg Thr Val Val Ser Leu Thr Gln
 900 905 910
 Glu Gln Lys Phe Glu His Met Tyr Ala Gln Ser Leu Gln Val Pro Tyr
 915 920 925
 Arg Asn Ser Leu Arg Lys Ala His Ile Phe Gly Ile Thr Phe Ser Phe
 930 935 940
 Thr Gln Ala Met Met Tyr Phe Ser Tyr Ala Gly Cys Phe Arg Phe Gly
 945 950 955 960
 Ala Tyr Leu Val Ala His Lys Leu Met Ser Phe Glu Asp Val Leu Leu
 965 970 975
 Val Phe Ser Ala Val Val Phe Gly Ala Met Ala Val Gly Gln Val Ser
 980 985 990
 Ser Phe Ala Pro Asp Tyr Ala Lys Ala Lys Ile Ser Ala Ala His Ile
 995 1000 1005
 Ile Met Ile Ile Glu Lys Thr Pro Leu Ile Asp Ser Tyr Ser Thr Glu
 1010 1015 1020
 Gly Leu Met Pro Asn Thr Leu Glu Gly Asn Val Thr Phe Gly Glu Val
 1025 1030 1035 1040
 Val Phe Asn Tyr Pro Thr Arg Pro Asp Ile Pro Val Leu Gln Gly Leu
 1045 1050 1055
 Ser Leu Glu Val Lys Lys Gly Gln Thr Leu Ala Leu Val Gly Ser Ser
 1060 1065 1070
 Gly Cys Gly Lys Ser Thr Val Val Gln Leu Leu Glu Arg Phe Tyr Asp
 1075 1080 1085
 Pro Leu Ala Gly Lys Val Leu Leu Asp Gly Lys Glu Ile Lys Arg Leu
 1090 1095 1100
 Asn Val Gln Trp Leu Arg Ala His Leu Gly Ile Val Ser Gln Glu Pro
 1105 1110 1115 1120
 Ile Leu Phe Asp Cys Ser Ile Ala Glu Asn Ile Ala Tyr Gly Asp Asn
 1125 1130 1135
 Ser Arg Val Val Ser Gln Glu Glu Ile Val Arg Ala Ala Lys Glu Ala
 1140 1145 1150
 Asn Ile His Ala Phe Ile Glu Ser Leu Pro Asn Lys Tyr Ser Thr Lys
 1155 1160 1165
 Val Gly Asp Lys Gly Thr Gln Leu Ser Gly Gly Gln Lys Gln Arg Ile
 1170 1175 1180
 Ala Ile Ala Arg Ala Leu Val Arg Gln Pro His Ile Leu Leu Leu Asp
 1185 1190 1195 1200
 Glu Ala Thr Ser Ala Leu Asp Thr Glu Ser Glu Lys Val Val Gln Glu
 1205 1210 1215
 Ala Leu Asp Lys Ala Arg Glu Gly Arg Thr Cys Ile Val Ile Ala His
 1220 1225 1230
 Arg Leu Ser Thr Ile Gln Asn Ala Asp Leu Ile Val Val Phe Gln Asn
 1235 1240 1245

Gly Arg Val Lys Glu His Gly Thr His Gln Gln Leu Leu Ala Gln Lys
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 <213> Mus musculus

<300>
 <308> Genbank P06795
 <309> 1998-07-15

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 35 40 45
 Phe Phe His Ala Ile Met Asn Gln Glu Ile Gly Trp Phe Asp Val His
 50 55 60
 Asp Val Gly Glu Leu Asn Thr Arg Leu Thr Asp Asp Val Ser Lys Ile
 65 70 75 80
 Asn Asp Gly Ile Gly Asp Lys Ile Gly Met Phe Phe Gln Ser Ile Thr
 85 90 95
 Thr Phe Leu Ala Gly Phe Ile Ile Gly Phe Ile Ser Gly Trp Lys Leu
 100 105 110
 Thr Leu Val Ile Leu Ala Val Ser Pro Leu Ile Gly Leu Ser Ser Ala
 115 120 125
 Leu Trp Ala Lys Val Leu Thr Ser Phe Thr Asn Lys Glu Leu Gln Ala
 130 135 140
 Tyr Ala Lys Ala Gly Ala Val Ala Glu Glu Val Leu Ala Ala Ile Arg
 145 150 155 160
 Thr Val Ile Ala Phe Gly Gly Gln Gln Lys Glu Leu Glu Arg Tyr Asn
 165 170 175
 Lys Asn Leu Glu Ala Lys Asn Val Gly Ile Lys Lys Ala Ile Thr
 180 185 190
 Ala Ser Ile Ser Ile Gly Ile Ala Tyr Leu Leu Val Tyr Ala Ser Tyr
 195 200 205
 Ala Leu Ala Phe Trp Tyr Gly Thr Ser Leu Val Leu Ser Asn Glu Tyr
 210 215 220
 Ser Ile Gly Glu Val Leu Thr Val Phe Phe Ser Ile Leu Leu Gly Thr
 225 230 235 240
 Phe Ser Ile Gly His Leu Ala Pro Asn Ile Glu Ala Phe Ala Asn Ala
 245 250 255
 Arg Gly Ala Ala Phe Glu Ile Phe Lys Ile Ile Asp Asn Glu Pro Ser
 260 265 270
 Ile Asp Ser Phe Ser Thr Lys Gly Tyr Lys Pro Asp Ser Ile Met Gly
 275 280 285
 Asn Leu Glu Phe Lys Asn Val His Phe Asn Tyr Pro Ser Arg Ser Glu
 290 295 300
 Val Gln Ile Leu Lys Gly Leu Asn Leu Lys Val Lys Ser Gly Gln Thr
 305 310 315 320
 Val Ala Leu Val Gly Asn Ser Gly Cys Gly Lys Ser Thr Thr Val Gln
 325 330 335
 Leu Met Gln Arg Leu Tyr Asp Pro Leu Glu Gly Val Val Ser Ile Asp
 340 345 350
 Gly Gln Asp Ile Arg Thr Ile Asn Val Arg Tyr Leu Arg Glu Ile Ile
 355 360 365
 Gly Val Val Ser Gln Glu Pro Val Leu Phe Ala Thr Thr Ile Ala Glu

370	375	380
Asn Ile Arg Tyr Gly Arg Glu Asp Val Thr Met Asp Glu Ile Glu Lys		
385	390	395
Ala Val Lys Glu Ala Asn Ala Tyr Asp Phe Ile Met Lys Leu Pro His		400
	405	410
Gln Phe Asp Thr Leu Val Gly Glu Arg Gly Ala Gln Leu Ser Gly Gly		415
	420	425
Gln Lys Gln Arg Ile Ala Ile Ala Arg Ala Leu Val Arg Asn Pro Lys		430
	435	440
Ile Leu Leu Leu Asp Glu Ala Thr Ser Ala Leu Asp Thr Glu Ser Glu		445
	450	455
Ala Val Val Gln Ala Ala Leu Asp Lys Ala Arg Glu Gly Arg Thr Thr		460
465	470	475
Ile Val Ile Ala His Arg Leu Ser Thr Val Arg Asn Ala Asp Val Ile		480
	485	490
Ala Gly Phe Asp Gly Gly Val Ile Val Glu Gln Gly Asn His Asp Glu		495
	500	505
Leu Met Arg Glu Lys Gly Ile Tyr Phe Lys Leu Val Met Thr Gln Thr		510
	515	520
Arg Gly Asn Glu Ile Glu Pro Gly Asn Asn Ala Tyr Gly Ser Gln Ser		525
	530	535
Asp Thr Asp Ala Ser Glu Leu Thr Ser Glu Glu Ser Lys Ser Pro Leu		540
545	550	555
Ile Arg Arg Ser Ile Tyr Arg Ser Val His Arg Lys Gln Asp Gln Glu		560
	565	570
Arg Arg Leu Ser Met Lys Glu Ala Val Asp Glu Asp Val Pro Leu Val		575
	580	585
Ser Phe Trp Arg Ile Leu Asn Leu Asn Leu Ser Glu Trp Pro Tyr Leu		590
	595	600
Leu Val Gly Val Leu Cys Ala Val Ile Asn Gly Cys Ile Gln Pro Val		605
	610	615
Phe Ala Ile Val Phe Ser Arg Ile Val Gly Val Phe Ser Arg Asp Asp		620
625	630	635
Asp His Glu Thr Lys Arg Gln Asn Cys Asn Leu Phe Ser Leu Phe Phe		640
	645	650
Leu Val Met Gly Leu Ile Ser Phe Val Thr Tyr Phe Phe Gln Gly Phe		655
	660	665
Thr Phe Gly Lys Ala Gly Glu Ile Leu Thr Lys Arg Val Arg Tyr Met		670
	675	680
Val Phe Lys Ser Met Leu Arg Gln Asp Ile Ser Trp Phe Asp Asp His		685
	690	695
Lys Asn Ser Thr Gly Ser Leu Thr Thr Arg Leu Ala Ser Asp Ala Ser		700
705	710	715
Ser Val Lys Gly Ala Met Gly Ala Arg Leu Ala Val Val Thr Gln Asn		720
	725	730
Val Ala Asn Leu Gly Thr Gly Val Ile Leu Ser Leu Val Tyr Gly Trp		735
	740	745
Gln Leu Thr Leu Leu Leu Val Val Ile Ile Pro Leu Ile Val Leu Gly		750
	755	760
Gly Ile Ile Glu Met Lys Leu Leu Ser Gly Gln Ala Leu Lys Asp Lys		765
	770	775
Lys Gln Leu Glu Ile Ser Gly Lys Ile Ala Thr Glu Ala Ile Glu Asn		780
785	790	795
Phe Arg Thr Ile Val Ser Leu Thr Arg Glu Gln Lys Phe Glu Thr Met		800
	805	810
Tyr Ala Gln Ser Leu Gln Val Pro Tyr Arg Asn Ala Met Lys Lys Ala		815
	820	825
His Val Phe Gly Ile Thr Phe Ser Phe Thr Gln Ala Met Met Tyr Phe		830
	835	840
Ser Tyr Ala Ala Cys Phe Arg Phe Gly Ala Tyr Leu Val Ala Gln Gln		845
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10.

[illegible]

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<212> PRT
<213> Homo sapiens
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<300>
<308> Genbank P21439
<309> 1998-07-15

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Ser	Ala	Ala	Val	Trp	Ala	Lys	Ile	Leu	Ser	Ala	Phe	Ser	Asp	Lys	Glu
			20					25					30		
Leu	Ala	Ala	Tyr	Ala	Lys	Ala	Gly	Ala	Val	Ala	Glu	Glu	Ala	Leu	Gly
		35					40					45			
Ala	Ile	Arg	Thr	Val	Ile	Ala	Phe	Gly	Gly	Gln	Asn	Lys	Glu	Leu	Glu
	50					55				60					
Arg	Tyr	Gln	Lys	His	Leu	Glu	Asn	Ala	Lys	Glu	Ile	Gly	Ile	Lys	Lys
65					70					75				80	
Ala	Ile	Ser	Ala	Asn	Ile	Ser	Met	Gly	Ile	Ala	Phe	Leu	Leu	Ile	Tyr
				85					90					95	

Ala	Ser	Tyr	Ala	Leu	Ala	Phe	Trp	Tyr	Gly	Ser	Thr	Leu	Val	Ile	Ser
			100					105					110		
Lys	Glu	Tyr	Thr	Ile	Gly	Asn	Ala	Met	Thr	Val	Phe	Phe	Ser	Ile	Leu
		115				120					125				
Ile	Gly	Ala	Phe	Ser	Val	Gly	Gln	Ala	Ala	Pro	Cys	Ile	Asp	Ala	Phe
	130					135					140				
Ala	Asn	Ala	Arg	Gly	Ala	Tyr	Val	Ile	Phe	Asp	Ile	Ile	Asp	Asn	
145				150					155					160	
Asn	Pro	Lys	Ile	Asp	Ser	Phe	Ser	Glu	Arg	Gly	His	Lys	Pro	Asp	Ser
			165					170					175		
Ile	Lys	Gly	Asn	Leu	Glu	Phe	Asn	Asp	Val	His	Phe	Ser	Tyr	Pro	Ser
		180						185					190		
Arg	Ala	Asn	Val	Lys	Ile	Leu	Lys	Gly	Leu	Asn	Leu	Lys	Val	Gln	Ser
		195					200					205			
Gly	Gln	Thr	Val	Ala	Leu	Val	Gly	Ser	Ser	Gly	Cys	Gly	Lys	Ser	Thr
	210					215					220				
Thr	Val	Gln	Leu	Ile	Gln	Arg	Leu	Tyr	Asp	Pro	Asp	Glu	Gly	Thr	Ile
225				230					235						240
Asn	Ile	Asp	Gly	Gln	Asp	Ile	Arg	Asn	Phe	Asn	Val	Asn	Tyr	Leu	Arg
			245					250					255		
Glu	Ile	Ile	Gly	Val	Val	Ser	Gln	Glu	Pro	Val	Leu	Phe	Ser	Thr	Thr
		260						265					270		
Ile	Ala	Glu	Asn	Ile	Cys	Tyr	Gly	Arg	Gly	Asn	Val	Thr	Met	Asp	Glu
	275					280					285				
Ile	Lys	Lys	Ala	Val	Lys	Glu	Ala	Asn	Ala	Tyr	Glu	Phe	Ile	Met	Lys
	290					295					300				
Leu	Pro	Gln	Lys	Phe	Asp	Thr	Leu	Val	Gly	Glu	Arg	Gly	Ala	Gln	Leu
305				310					315					320	
Ser	Gly	Gly	Gln	Lys	Gln	Arg	Ile	Ala	Ile	Ala	Arg	Ala	Leu	Val	Arg
			325					330					335		
Asn	Pro	Lys	Ile	Leu	Leu	Leu	Asp	Glu	Ala	Thr	Ser	Ala	Leu	Asp	Thr
		340						345					350		
Glu	Ser	Glu	Ala	Glu	Val	Gln	Ala	Ala	Leu	Asp	Lys	Ala	Arg	Glu	Gly
	355					360						365			
Arg	Thr	Thr	Ile	Val	Ile	Ala	His	Arg	Leu	Ser	Thr	Val	Arg	Asn	Ala
	370					375						380			
Asp	Val	Ile	Ala	Gly	Phe	Glu	Asp	Gly	Val	Ile	Val	Glu	Gln	Gly	Ser
385				390						395					400
His	Ser	Glu	Leu	Met	Lys	Lys	Glu	Gly	Val	Tyr	Phe	Lys	Leu	Val	Asn
			405					410					415		
Met	Gln	Thr	Ser	Gly	Ser	Gln	Ile	Gln	Ser	Glu	Glu	Phe	Glu	Leu	Asn
		420						425					430		
Asp	Glu	Lys	Ala	Ala	Thr	Arg	Met	Ala	Pro	Asn	Gly	Trp	Lys	Ser	Arg
	435					440						445			
Leu	Phe	Arg	His	Ser	Thr	Gln	Lys	Asn	Leu	Lys	Asn	Ser	Gln	Met	Cys
	450					455					460				
Gln	Lys	Ser	Leu	Asp	Val	Glu	Thr	Asp	Gly	Leu	Glu	Ala	Asn	Val	Pro
465				470					475						480
Pro	Val	Ser	Phe	Leu	Lys	Val	Leu	Lys	Leu	Asn	Lys	Thr	Glu	Trp	Pro
			485					490					495		
Tyr	Phe	Val	Val	Gly	Thr	Val	Cys	Ala	Ile	Ala	Asn	Gly	Gly	Leu	Gln
		500						505					510		
Pro	Ala	Phe	Ser	Val	Ile	Phe	Ser	Glu	Ile	Ile	Ala	Ile	Phe	Gly	Pro
	515					520						525			
Gly	Asp	Asp	Ala	Val	Lys	Gln	Gln	Lys	Cys	Asn	Ile	Phe	Ser	Leu	Ile
	530					535					540				
Phe	Leu	Phe	Leu	Gly	Ile	Ile	Ser	Phe	Phe	Thr	Phe	Phe	Leu	Gln	Gly
545				550					555						560
Phe	Thr	Phe	Gly	Lys	Ala	Gly	Glu	Ile	Leu	Thr	Arg	Arg	Leu	Arg	Ser
			565					570					575		
Met	Ala	Phe	Lys	Ala	Met	Leu	Arg	Gln	Asp	Met	Ser	Trp	Phe	Asp	Asp
			580					585					590		

His Lys Asn Ser Thr Gly Ala Leu Ser Thr Arg Leu Ala Thr Asp Ala
 595 600 605
 Ala Gln Val Gln Gly Ala Thr Gly Thr Arg Leu Ala Leu Ile Ala Gln
 610 615 620
 Asn Ile Ala Asn Leu Gly Thr Gly Ile Ile Ile Ser Phe Ile Tyr Gly
 625 630 635 640
 Trp Gln Leu Thr Leu Leu Leu Leu Ala Val Val Pro Ile Ile Ala Val
 645 650 655
 Ser Gly Ile Val Glu Met Lys Leu Leu Ala Gly Asn Ala Lys Arg Asp
 660 665 670
 Lys Lys Glu Leu Glu Ala Ala Gly Lys Ile Ala Thr Glu Ala Ile Glu
 675 680 685
 Asn Ile Arg Thr Val Val Ser Leu Thr Gln Glu Arg Lys Phe Glu Ser
 690 695 700
 Met Tyr Val Glu Lys Leu Tyr Gly Pro Tyr Arg Asn Ser Val Gln Lys
 705 710 715 720
 Ala His Ile Tyr Gly Ile Thr Phe Ser Ile Ser Gln Ala Phe Met Tyr
 725 730 735
 Phe Ser Tyr Ala Gly Cys Phe Arg Phe Gly Ala Tyr Leu Ile Val Asn
 740 745 750
 Gly His Met Arg Phe Arg Asp Val Ile Leu Val Phe Ser Ala Ile Val
 755 760 765
 Phe Gly Ala Val Ala Leu Gly His Ala Ser Ser Phe Ala Pro Asp Tyr
 770 775 780
 Ala Lys Ala Lys Leu Ser Ala Ala His Leu Phe Met Leu Phe Glu Arg
 785 790 795 800
 Gln Pro Leu Ile Asp Ser Tyr Ser Glu Glu Gly Leu Lys Pro Asp Lys
 805 810 815
 Phe Glu Gly Asn Ile Thr Phe Asn Glu Val Val Phe Asn Tyr Pro Thr
 820 825 830
 Arg Ala Asn Val Pro Val Leu Gln Gly Leu Ser Leu Glu Val Lys Lys
 835 840 845
 Gly Gln Thr Leu Ala Leu Val Gly Ser Ser Gly Cys Gly Lys Ser Thr
 850 855 860
 Val Val Gln Leu Leu Glu Arg Phe Tyr Asp Pro Leu Ala Gly Thr Val
 865 870 875 880
 Leu Leu Asp Gly Gln Glu Ala Lys Lys Leu Asn Val Gln Trp Leu Arg
 885 890 895
 Ala Gln Leu Gly Ile Val Ser Gln Glu Pro Ile Leu Phe Asp Cys Ser
 900 905 910
 Ile Ala Glu Asn Ile Ala Tyr Gly Asp Asn Ser Arg Val Val Ser Gln
 915 920 925
 Asp Glu Ile Val Ser Ala Ala Lys Ala Ala Asn Ile His Pro Phe Ile
 930 935 940
 Glu Thr Leu Pro His Lys Tyr Glu Thr Arg Val Gly Asp Lys Gly Thr
 945 950 955 960
 Gln Leu Ser Gly Gly Gln Lys Gln Arg Ile Ala Ile Ala Arg Ala Leu
 965 970 975
 Ile Arg Gln Pro Gln Ile Leu Leu Leu Asp Glu Ala Thr Ser Ala Leu
 980 985 990
 Asp Thr Glu Ser Glu Lys Val Val Gln Glu Ala Leu Asp Lys Ala Arg
 995 1000 1005
 Glu Gly Arg Thr Cys Ile Val Ile Ala His Arg Leu Ser Thr Ile Gln
 1010 1015 1020
 Asn Ala Asp Leu Ile Val Val Phe Gln Asn Gly Arg Val Lys Glu His
 1025 1030 1035 1040
 Gly Thr His Gln Gln Leu Leu Ala Gln Lys Gly Ile Tyr Phe Ser Met
 1045 1050 1055
 Val Ser Val Gln Ala Gly Thr Gln Asn Leu
 1060 1065

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 <213> Mus musculus

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 <309> 1997-11-01

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 Leu Ala Ala Tyr Ala Lys Ala Gly Ala Val Ala Glu Glu Ala Pro Gly
 35 40 45
 Ala Ile Arg Thr Val Ile Ala Phe Gly Gly Gln Asn Lys Glu Leu Glu
 50 55 60
 Arg Tyr Gln Lys His Leu Glu Asn Ala Lys Lys Ile Gly Ile Lys Lys
 65 70 75 80
 Ala Ile Ser Ala Asn Ile Ser Met Gly Ile Ala Phe Leu Leu Ile Tyr
 85 90 95
 Ala Ser Tyr Ala Leu Ala Phe Trp Tyr Gly Ser Thr Leu Val Ile Ser
 100 105 110
 Lys Glu Tyr Thr Ile Gly Asn Ala Met Thr Val Phe Phe Ser Ile Leu
 115 120 125
 Ile Gly Ala Phe Ser Val Gly Gln Ala Ala Pro Cys Ile Asp Ala Phe
 130 135 140
 Ala Asn Ala Arg Gly Ala Ala Tyr Val Ile Phe Asp Ile Ile Asp Asn
 145 150 155 160
 Asn Pro Lys Ile Asp Ser Phe Ser Glu Arg Gly His Lys Pro Asp Asn
 165 170 175
 Ile Lys Gly Asn Leu Glu Phe Ser Asp Val His Phe Ser Tyr Pro Ser
 180 185 190
 Arg Ala Asn Ile Lys Ile Leu Lys Gly Leu Asn Leu Lys Val Lys Ser
 195 200 205
 Gly Gln Thr Val Ala Leu Val Gly Asn Ser Gly Cys Gly Lys Ser Thr
 210 215 220
 Thr Val Gln Leu Leu Gln Arg Leu Tyr Asp Pro Thr Glu Gly Lys Ile
 225 230 235 240
 Ser Ile Asp Gly Gln Asp Ile Arg Asn Phe Asn Val Arg Cys Leu Arg
 245 250 255
 Glu Ile Ile Gly Val Val Ser Gln Glu Pro Val Leu Phe Ser Thr Thr
 260 265 270
 Ile Ala Glu Asn Ile Arg Tyr Gly Arg Gly Asn Val Thr Met Asp Glu
 275 280 285
 Ile Glu Lys Ala Val Lys Glu Ala Asn Ala Tyr Asp Phe Ile Met Lys
 290 295 300
 Leu Pro Gln Lys Phe Asp Thr Leu Val Gly Asp Arg Gly Ala Gln Leu
 305 310 315 320
 Ser Gly Gly Gln Lys Gln Arg Ile Ala Ile Ala Arg Ala Leu Val Arg
 325 330 335
 Asn Pro Lys Ile Leu Leu Leu Asp Glu Ala Thr Ser Ala Leu Asp Thr
 340 345 350
 Glu Ser Glu Ala Glu Val Gln Ala Ala Leu Asp Lys Ala Arg Glu Gly
 355 360 365
 Arg Thr Thr Ile Val Ile Ala His Arg Leu Ser Thr Ile Arg Asn Ala
 370 375 380
 Asp Val Ile Ala Gly Phe Glu Asp Gly Val Ile Val Glu Gln Gly Ser
 385 390 395 400
 His Ser Glu Leu Met Lys Lys Glu Gly Ile Tyr Phe Arg Leu Val Asn
 405 410 415
 Met Gln Thr Ala Gly Ser Gln Ile Leu Ser Glu Glu Phe Glu Ala Arg

14.

Ala	Leu	Val	420	Asn	Pro	Lys	Ile	425	Leu	Leu	Leu	Asp	Glu	Ala	Thr	Ser
			435					440						445		
Ala	Leu	Asp	Thr	Glu	Ser	Glu	Ala	Val	Val	Gln	Val	Ala	Leu	Asp	Lys	
			450				455					460				
Ala	Arg	Lys	Gly	Arg	Thr	Thr	Ile	Val	Ile	Ala	His	Arg	Leu	Ser	Thr	
465					470						475				480	
Val	Arg	Asn	Ala	Asp	Val	Ile	Ala	Gly	Phe	Asp	Asp	Gly	Val	Ile	Val	
				485					490					495		
Glu	Lys	Gly	Asn	His	Asp	Glu	Leu	Met	Lys	Glu	Lys	Gly	Ile	Tyr	Phe	
			500					505					510			
Lys	Leu	Val	Thr	Met	Gln	Thr	Ala	Gly	Asn	Glu	Val	Glu	Leu	Glu	Asn	
			515					520					525			
Ala	Ala	Ala	Arg	Ala	Leu	Val	Arg	Asn	Pro	Lys	Ile	Leu	Leu	Leu	Asp	
			530				535					540				
Glu	Ala	Thr	Ser	Ala	Leu	Asp	Thr	Glu	Ser	Glu	Ala	Val	Val	Gln	Ala	
545					550						555				560	
Ala	Leu	Asp	Lys	Ala	Arg	Glu	Gly	Arg	Thr	Thr	Ile	Val	Ile	Ala	His	
				565				570						575		
Arg	Leu	Ser	Thr	Val	Arg	Asn	Ala	Asp	Val	Ile	Ala	Gly	Phe	Asp	Gly	
			580					585					590			
Gly	Val	Ile	Val	Glu	Gln	Gly	Asn	His	Asp	Glu	Leu	Met	Arg	Glu	Lys	
			595				600					605				
Gly	Ile	Tyr	Phe	Lys	Leu	Val	Met	Thr	Gln	Thr	Arg	Gly	Asn	Glu	Ile	
			610				615					620				
Glu	Pro	Gly	Asn	Asn	Ala	Val	Glu	Leu	Ser	Asp	Glu	Lys	Ala	Ala	Gly	
625					630						635				640	
Asp	Val	Ala	Pro	Asn	Gly	Trp	Lys	Ala	Arg	Ile	Phe	Arg	Asn	Ser	Thr	
				645					650					655		
Lys	Lys	Ser	Leu	Lys	Ser	Pro	His	Gln	Asn	Arg	Leu	Asp	Glu	Glu	Thr	
			660					665					670			
Asn	Glu	Leu	Asp	Ala	Asn	Val	Pro	Pro	Val	Ser	Phe	Leu	Lys	Val	Leu	
			675				680					685				
Lys	Leu	Asn	Lys	Thr	Glu	Trp	Pro	Tyr	Phe	Val	Val	Gly	Thr	Val	Cys	
			690				695					700				
Ala	Ile	Ala	Asn	Gly	Ala	Leu	Gln	Pro	Ala	Phe	Ser	Ile	Ile	Leu	Ser	
705					710						715				720	
Glu	Met	Ile	Ala	Ile	Phe	Gly	Pro	Gly	Asp	Asp	Ala	Val	Lys	Gln	Gln	
				725					730					735		
Lys	Cys	Asn	Met	Phe	Ser	Leu	Val	Phe	Leu	Gly	Leu	Gly	Val	Leu	Ser	
				740				745					750			
Phe	Phe	Thr	Phe	Phe	Leu	Gln	Gly	Phe	Thr	Phe	Gly	Lys	Ala	Gly	Glu	
			755				760					765				
Ile	Leu	Thr	Thr	Arg	Leu	Arg	Ser	Met	Ala	Phe	Lys	Ala	Met	Leu	Arg	
					775						780					
Gln	Asp	Met	Ser	Trp	Phe	Asp	Asp	His	Lys	Asn	Ser	Thr	Gly	Ala	Leu	
785					790						795				800	
Ser	Thr	Arg	Leu	Ala	Thr	Asp	Ala	Ala	Gln	Val	Gln	Gly	Ala	Thr	Gly	
				805					810					815		
Thr	Lys	Leu	Ala	Leu	Ile	Ala	Gln	Asn	Thr	Ala	Asn	Leu	Gly	Thr	Gly	
				820				825					830			
Ile	Ile	Ile	Ser	Phe	Ile	Tyr	Gly	Trp	Gln	Leu	Thr	Leu	Leu	Leu	Leu	
			835				840					845				
Ser	Val	Val	Pro	Phe	Ile	Ala	Val	Ala	Gly	Ile	Val	Glu	Met	Lys	Met	
			850				855					860				
Leu	Ala	Gly	Asn	Ala	Lys	Arg	Asp	Lys	Lys	Glu	Met	Glu	Ala	Ala	Gly	
865					870						875				880	
Lys	Ile	Ala	Thr	Glu	Ala	Ile	Glu	Asn	Ile	Arg	Thr	Val	Val	Ser	Leu	
				885					890					895		
Thr	Gln	Glu	Arg	Lys	Phe	Glu	Ser	Met	Tyr	Val	Glu	Lys	Leu	His	Gly	
			900					905					910			
Pro	Tyr	Arg	Asn	Ser	Val	Arg	Lys	Ala	His	Ile	Tyr	Gly	Ile	Thr	Phe	

15.

915 920 925
 Ser Ile Ser Gln Ala Phe Met Tyr Phe Ser Tyr Ala Gly Cys Phe Arg
 930 935 940
 Phe Gly Ser Tyr Leu Ile Val Asn Gly His Met Arg Phe Lys Asp Val
 945 950 955 960
 Ile Leu Val Phe Ser Ala Ile Val Leu Gly Ala Val Ala Leu Gly His
 965 970 975
 Ala Ser Ser Phe Ala Pro Asp Tyr Ala Lys Ala Lys Leu Ser Ala Ala
 980 985 990
 Tyr Leu Phe Ser Leu Phe Glu Arg Gln Pro Leu Ile Asp Ser Tyr Ser
 995 1000 1005
 Gly Glu Gly Leu Trp Pro Asp Lys Phe Glu Gly Ser Val Thr Phe Asn
 1010 1015 1020
 Glu Val Val Phe Asn Tyr Pro Thr Arg Ala Asn Val Pro Val Leu Gln
 1025 1030 1035 1040
 Gly Leu Ser Leu Glu Val Lys Lys Gly Gln Thr Leu Ala Leu Val Gly
 1045 1050 1055
 Ser Ser Gly Cys Gly Lys Ser Thr Val Val Gln Leu Leu Glu Arg Phe
 1060 1065 1070
 Tyr Asp Pro Met Ala Gly Ser Val Leu Leu Asp Gly Gln Glu Ala Lys
 1075 1080 1085
 Lys Leu Asn Val Gln Trp Leu Arg Ala Gln Leu Gly Ile Val Ser Gln
 1090 1095 1100
 Glu Pro Ile Leu Phe Asp Cys Ser Ile Ala Glu Asn Ile Ala Tyr Gly
 1105 1110 1115 1120
 Asp Asn Ser Arg Val Val Pro His Asp Glu Ile Val Arg Ala Ala Lys
 1125 1130 1135
 Glu Ala Asn Ile His Pro Phe Ile Glu Thr Leu Pro Gln Lys Tyr Asn
 1140 1145 1150
 Thr Arg Val Gly Asp Lys Gly Thr Gln Leu Ser Gly Gly Gln Lys Gln
 1155 1160 1165
 Arg Ile Ala Ile Ala Arg Ala Leu Ile Arg Gln Pro Arg Val Leu Leu
 1170 1175 1180
 Leu Asp Glu Ala Thr Ser Ala Leu Asp Thr Glu Ser Glu Lys Val Val
 1185 1190 1195 1200
 Gln Glu Ala Leu Asp Lys Ala Arg Glu Gly Arg Thr Cys Ile Val Ile
 1205 1210 1215
 Ala His Arg Leu Ser Thr Ile Gln Asn Ala Asp Leu Ile Val Val Ile
 1220 1225 1230
 Glu Asn Gly Lys Val Lys Glu His Gly Thr His Gln Gln Leu Leu Ala
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 Asn Leu
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 <309> 1997-03-13

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 Met Trp Ser Gly Glu Arg Gln Thr Thr Lys Met Arg Ile Lys Tyr Leu
 35 40 45

16

Glu Ala Ala Leu Asn Gln Asp Ile Gln Phe Phe Asp Thr Glu Val Arg
 50 55 60
 Thr Ser Asp Val Val Phe Ala Ile Asn Thr Asp Ala Val Met Val Gln
 65 70 75 80
 Asp Ala Ile Ser Glu Lys Leu Gly Asn Phe Ile His Tyr Met Ala Thr
 85 90 95
 Phe Val Ser Gly Phe Ile Val Gly Phe Thr Ala Val Trp Gln Leu Ala
 100 105 110
 Leu Val Thr Leu Ala Val Val Pro Leu Ile Ala Val Ile Gly Gly Ile
 115 120 125
 His Thr Thr Thr Leu Ser Lys Leu Ser Asn Lys Ser Gln Glu Ser Leu
 130 135 140
 Ser Gln Ala Gly Asn Ile Val Glu Gln Thr Val Val Gln Ile Arg Val
 145 150 155 160
 Val Met Ala Phe Val Gly Glu Ser Arg Ala Ser Gln Ala Tyr Ser Ser
 165 170 175
 Ala Leu Lys Ile Ala Gln Lys Leu Gly Tyr Lys Thr Gly Leu Ala Lys
 180 185 190
 Gly Met Gly Leu Gly Ala Thr Tyr Phe Val Val Phe Cys Cys Tyr Ala
 195 200 205
 Leu Leu Leu Trp Tyr Gly Gly Tyr Leu Val Arg His His Leu Thr Asn
 210 215 220
 Gly Gly Leu Ala Ile Ala Thr Met Phe Ala Val Met Ile Gly Gly Leu
 225 230 235 240
 Ala Leu Gly Gln Ser Ala Pro Ser Met Ala Ala Phe Ala Lys Ala Lys
 245 250 255
 Val Ala Ala Ala Lys Ile Phe Arg Ile Ile Asp His Lys Pro Thr Ile
 260 265 270
 Glu Arg Asn Ser Glu Ser Gly Val Glu Leu Asp Ser Val Thr Gly Leu
 275 280 285
 Val Glu Leu Lys Asn Val Asp Phe Ser Tyr Pro Ser Arg Pro Asp Val
 290 295 300
 Lys Ile Leu Asn Asn Phe Cys Leu Ser Val Pro Ala Gly Lys Thr Ile
 305 310 315 320
 Ala Leu Val Gly Ser Ser Gly Ser Gly Lys Ser Thr Val Val Ser Leu
 325 330 335
 Ile Glu Arg Phe Tyr Asp Pro Asn Ser Gly Gln Val Leu Leu Asp Gly
 340 345 350
 Gln Asp Leu Lys Thr Leu Lys Leu Arg Trp Leu Arg Gln Gln Ile Gly
 355 360 365
 Leu Val Ser Gln Glu Pro Ala Leu Phe Ala Thr Ser Ile Lys Glu Asn
 370 375 380
 Ile Leu Leu Gly Arg Pro Asp Ala Asp Gln Val Glu Ile Glu Glu Ala
 385 390 395 400
 Ala Arg Val Ala Asn Ala His Ser Phe Ile Ile Lys Leu Pro Asp Gly
 405 410 415
 Phe Asp Thr Gln Val Gly Glu Arg Gly Leu Gln Leu Ser Gly Gly Gln
 420 425 430
 Lys Gln Arg Ile Ala Ile Ala Arg Ala Met Leu Lys Asn Pro Ala Ile
 435 440 445
 Leu Leu Leu Asp Glu Ala Thr Ser Ala Leu Asp Ser Glu Ser Glu Lys
 450 455 460
 Leu Val Gln Glu Ala Leu Asp Arg Phe Met Ile Gly Arg Thr Thr Leu
 465 470 475 480
 Ile Ile Ala His Arg Leu Ser Thr Ile Arg Lys Ala Asp Leu Val Ala
 485 490 495
 Val Leu Gln Gln Gly Ser Val Ser Glu Ile Gly Thr His Asp Glu Leu
 500 505 510
 Phe Ser Lys Gly Glu Asn Gly Val Tyr Ala Lys Leu Ile Lys Met Gln
 515 520 525
 Glu Ala Ala His Glu Thr Ala Met Ser Asn Ala Arg Lys Ser Ser Ala
 530 535 540

Arg Pro Ser Ser Ala Arg Asn Ser Val Ser Ser Pro Ile Met Thr Arg
 545 550 555 560
 Asn Ser Ser Tyr Gly Arg Ser Pro Tyr Ser Arg Arg Leu Ser Asp Phe
 565 570 575
 Ser Thr Ser Asp Phe Ser Leu Ser Ile Asp Ala Ser Ser Tyr Pro Asn
 580 585 590
 Tyr Arg Asn Glu Lys Leu Ala Phe Lys Asp Gln Ala Asn Ser Phe Trp
 595 600 605
 Arg Leu Ala Lys Met Asn Ser Pro Glu Trp Lys Tyr Ala Leu Leu Gly
 610 615 620
 Ser Val Gly Ser Val Ile Cys Gly Ser Leu Ser Ala Phe Phe Ala Tyr
 625 630 635 640
 Val Leu Ser Ala Val Leu Ser Val Tyr Tyr Asn Pro Asp His Glu Tyr
 645 650 655
 Met Ile Lys Gln Ile Asp Lys Tyr Cys Tyr Leu Leu Ile Gly Leu Ser
 660 665 670
 Ser Ala Ala Leu Val Phe Asn Thr Leu Gln His Ser Phe Trp Asp Ile
 675 680 685
 Val Gly Glu Asn Leu Thr Lys Arg Val Arg Glu Lys Met Leu Ser Ala
 690 695 700
 Val Leu Lys Asn Glu Met Ala Trp Phe Asp Gln Glu Glu Asn Glu Ser
 705 710 715 720
 Ala Arg Ile Ala Ala Arg Leu Ala Leu Asp Ala Asn Asn Val Arg Ser
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 Ala Ile Gly Asp Arg Ile Ser Val Ile Val Gln Asn Thr Ala Leu Met
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 Leu Val Ala Cys Thr Ala Gly Phe Val Leu Gln Trp Arg Leu Ala Leu
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 Val Leu Val Ala Val Phe Pro Val Val Val Ala Ala Thr Val Leu Gln
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 Ser Gly Tyr Gly Val Ala Gln Phe Cys Leu Tyr Ala Ser Tyr Ala Leu
 850 855 860
 Gly Leu Trp Tyr Ala Ser Trp Leu Val Lys His Gly Ile Ser Asp Phe
 865 870 875 880
 Ser Lys Thr Ile Arg Val Phe Met Val Leu Met Val Ser Ala Asn Gly
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 Ala Ala Glu Thr Leu Thr Leu Ala Pro Asp Phe Ile Lys Gly Gly Gln
 900 905 910
 Ala Met Arg Ser Val Phe Glu Leu Leu Asp Arg Lys Thr Glu Ile Glu
 915 920 925
 Pro Asp Asp Pro Asp Thr Thr Pro Val Pro Asp Arg Leu Arg Gly Glu
 930 935 940
 Val Glu Leu Lys His Ile Asp Phe Ser Tyr Pro Ser Arg Pro Asp Ile
 945 950 955 960
 Gln Ile Phe Arg Asp Leu Ser Leu Arg Ala Arg Ala Gly Lys Thr Leu
 965 970 975
 Ala Leu Val Gly Pro Ser Gly Cys Gly Lys Ser Ser Val Ile Ser Leu
 980 985 990
 Ile Gln Arg Phe Tyr Glu Pro Ser Ser Gly Arg Val Met Ile Asp Gly
 995 1000 1005
 Lys Asp Ile Arg Lys Tyr Asn Leu Lys Ala Ile Arg Lys His Ile Ala
 1010 1015 1020
 Ile Val Pro Gln Glu Pro Cys Leu Phe Gly Thr Thr Ile Tyr Glu Asn
 1025 1030 1035 1040

18

Ile Ala Tyr Gly His Glu Cys Ala Thr Glu Ala Glu Ile Ile Gln Ala
 1045 1050 1055
 Ala Thr Leu Ala Ser Ala His Lys Phe Ile Ser Ala Leu Pro Glu Gly
 1060 1065 1070
 Tyr Lys Thr Tyr Val Gly Glu Arg Gly Val Gln Leu Ser Gly Gly Gln
 1075 1080 1085
 Lys Gln Arg Ile Ala Ile Ala Arg Ala Leu Val Arg Lys Ala Glu Ile
 1090 1095 1100
 Met Leu Leu Asp Glu Ala Thr Ser Ala Leu Asp Ala Glu Ser Glu Arg
 1105 1110 1115 1120
 Ser Val Gln Glu Ala Leu Asp Gln Ala Cys Ser Gly Arg Thr Ser Ile
 1125 1130 1135
 Val Val Ala His Arg Leu Ser Thr Ile Arg Asn Ala His Val Ile Ala
 1140 1145 1150
 Val Ile Asp Asp Gly Lys Val Ala Glu Gln Gly Ser His Ser His Leu
 1155 1160 1165
 Leu Lys Asn His Pro Asp Gly Ile Tyr Ala Arg Met Ile Gln Leu Gln
 1170 1175 1180
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 Arg Val Lys Glu Asp Asp Ala
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 <309> 1997-05-19

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 35 40 45
 Arg Ser Met Leu Ser Gln Asp Ile Ser Leu Phe Asp Thr Glu Ala Ser
 50 55 60
 Thr Gly Glu Val Ile Ser Ala Ile Thr Ser Asp Ile Leu Val Val Gln
 65 70 75 80
 Asp Ala Leu Ser Glu Lys Val Gly Asn Phe Leu His Tyr Ile Ser Arg
 85 90 95
 Phe Ile Ala Gly Phe Ala Ile Gly Phe Thr Ser Val Trp Gln Ile Ser
 100 105 110
 Leu Val Thr Leu Ser Ile Val Pro Leu Ile Ala Leu Ala Gly Gly Ile
 115 120 125
 Tyr Ala Phe Val Ala Ile Gly Leu Ile Ala Arg Val Arg Lys Ser Tyr
 130 135 140
 Ile Lys Ala Gly Glu Ile Ala Glu Glu Val Ile Gly Asn Val Arg Thr
 145 150 155 160
 Val Gln Ala Phe Thr Gly Glu Glu Arg Ala Val Arg Leu Tyr Arg Glu
 165 170 175
 Ala Leu Glu Asn Thr Tyr Lys Tyr Gly Arg Lys Ala Gly Leu Thr Lys
 180 185 190
 Gly Leu Gly Leu Gly Ser Met His Cys Val Leu Phe Leu Ser Trp Ala
 195 200 205
 Leu Leu Val Trp Phe Thr Ser Val Val Val His Lys Asp Ile Ala Asp
 210 215 220
 Gly Gly Lys Ser Phe Thr Thr Met Leu Asn Val Val Ile Ala Gly Leu

225 230 235 240
 Ser Leu Gly Gln Ala Ala Pro Asp Ile Ser Ala Phe Val Arg Ala Lys
 245 250 255
 Ala Ala Ala Tyr Pro Ile Phe Lys Met Ile Glu Arg Asn Thr Val Thr
 260 265 270
 Lys Thr Ser Ala Lys Ser Gly Arg Lys Leu Gly Lys Val Asp Gly His
 275 280 285
 Ile Gln Phe Lys Asp Ala Thr Phe Ser Tyr Pro Ser Arg Pro Asp Val
 290 295 300
 Val Ile Phe Asp Arg Leu Asn Leu Ala Ile Pro Ala Gly Lys Ile Val
 305 310 315 320
 Ala Leu Val Gly Gly Ser Gly Ser Gly Lys Ser Thr Val Ile Ser Leu
 325 330 335
 Ile Glu Arg Phe Tyr Glu Pro Ile Ser Gly Ala Val Leu Leu Asp Gly
 340 345 350
 Asn Asn Ile Ser Glu Leu Asp Ile Lys Trp Leu Arg Gly Gln Ile Gly
 355 360 365
 Leu Val Asn Gln Glu Pro Ala Leu Phe Ala Thr Thr Ile Arg Glu Asn
 370 375 380
 Ile Leu Tyr Gly Lys Asp Asp Ala Thr Ala Glu Glu Ile Thr Arg Ala
 385 390 395 400
 Ala Lys Leu Ser Glu Ala Ile Ser Phe Ile Asn Asn Leu Pro Glu Gly
 405 410 415
 Phe Glu Thr Gln Val Gly Glu Arg Gly Ile Gln Leu Ser Gly Gly Gln
 420 425 430
 Lys Gln Arg Ile Ala Ile Ser Arg Ala Ile Val Lys Asn Pro Ser Ile
 435 440 445
 Leu Leu Leu Asp Glu Ala Thr Ser Ala Leu Asp Ala Glu Ser Glu Lys
 450 455 460
 Ser Val Gln Glu Ala Leu Asp Arg Val Met Val Gly Arg Thr Thr Val
 465 470 475 480
 Val Val Ala His Arg Leu Ser Thr Val Arg Asn Ala Asp Ile Ile Ala
 485 490 495
 Val Val His Glu Gly Lys Ile Val Glu Phe Gly Asn His Glu Asn Leu
 500 505 510
 Ile Ser Asn Pro Asp Gly Ala Tyr Ser Ser Leu Leu Arg Leu Gln Glu
 515 520 525
 Thr Ala Ser Leu Gln Arg Asn Pro Ser Leu Asn Arg Thr Leu Ser Arg
 530 535 540
 Pro His Ser Ile Lys Tyr Ser Arg Glu Leu Ser Arg Thr Arg Ser Ser
 545 550 555 560
 Phe Cys Ser Glu Arg Glu Ser Val Thr Arg Pro Asp Gly Ala Asp Pro
 565 570 575
 Ser Lys Lys Val Lys Val Thr Val Gly Arg Leu Tyr Ser Met Ile Arg
 580 585 590
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22.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/22363

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 800/278, 294, 300; 435/69.1, 71.2, 468, 419, 252.3; 320.1; 536/23.6, 24.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	DUDLER ET AL. Structure of an mdr-like Gene from Arabidopsis thaliana. The Journal of Biological Chemistry. March 1992, Vol. 267, No. 9, pages 5882-5888, see pages 5883, 5885, and 5888.	24, 29-30 ----- 1-6
Y	CHO et al. An Anion Channel in Arabidopsis Hypocotyls Activited by Blue Light. Proc. Natl. Acad. Sci. USA. July 1996, Vol. 93, pages 8134-8138, see page 8134.	1-2
X --- Y	EMYR DAVIES et al. Cloning and Characterization of a Novel P-Glycoprotein Homologue from Barley. Gene. June 1997, Vol. 199, pages 195-202, see whole document.	24, 29-30 ----- 1-6

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principles or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

23 DECEMBER 1999

Date of mailing of the international search report

27 JAN 2000

 Name and mailing address of the ISA/US
 Commissioner of Patents and Trademarks
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 Washington, D.C. 20231

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/22363

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P ----- Y,P	SIDLER et al. Involvement of an ABC Transporter in a Developmental Pathway Regulating Hypocotyl Cell Elongation in the Light. The Plant Cell. October 1998, Vol. 10, pages 1623-1636, see pages 1623 and 1629-1634.	24, 28-31 ----- 1-6, 9-23
Y	TOMMASINI et al. Differential Expression of Genes Coding for ABC Transporters after Treatment of Arabidopsis thaliana with Xenobiotics. FEBS Letters. May 1997, Vol. 411, pages 206-210, see page 206.	1-6, 24
A	US 5,786, 162 A (CORBISIER et al) 28 July 1998, see whole document.	1-6, 9-24, 28-31
A	US 5,073,677 A (HELMER et al) 17 December 1991, see whole document.	1-6, 9-24, 28-31

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/22363

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-6, 9-24, 28-31

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/22363

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

C12N 5/04, 15/00, 15/09, 15/11, 15/29, 15/63, 15/74, 15/81, 15/82 ; A01H 5/00

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

800/278, 294, 300; 435/69.1, 71.2, 468, 419, 252.3, 320.1; 536/23.6, 24.1

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

DIALOG, WEST1.2a

SEARCH TERMS: MDR-LIKE GENES, P-GLYCOPROTEIN GENES, ARABIDOPSIS, NPPB, XENOBIOTIC, RESISTANT PLANTS, ABC TRANSPORTER, A₁GP1 EXPRESSION, TRANSGENIC PLANT

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-6, 9-24, 28-31, drawn to an isolated nucleic acid in a recombinant expression cassette, a vector comprising it, a transgenic plant, and a method for producing a plant with enhanced resistance to xenobiotic compounds.

Group II, claim(s) 7-8, 25-26, 32-38, drawn to an isolated protein and antibodies for the protein.

Group III, claim(s) 27, drawn to an oligonucleotide.

Group IV, claim(s) 39-40, drawn to P-glycoprotein gene promoter.

Group V, claim(s) 41-45, drawn to a plant with mutated pIPAC gene and a method of making it.

The inventions listed as Groups I-V do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The claimed isolated nucleic acid molecules and transformed cells are anticipated by each of Dudler et al, Emyr Davis et al, and Sidler et al, as set forth in the Search Report, and so do not constitute a single special technical feature which would be an advance over the prior art.

The invention of Group I, drawn to a first product and process of use, requires an isolated nucleic acid encoding P-glycoprotein, a vector, host cells, and a method for plant transformation and regeneration not required by any other group.

The invention of Group II, drawn to a second product, requires an isolated polypeptide and antibodies for the polypeptide not required by any other group.

The invention of Group III, drawn to a third product, requires an oligonucleotide and a hybridization technique not required by any other group.

The invention of Group IV, drawn to a fourth product, requires a specific gene promoter not required by any other group.

The invention of Group V, drawn to a fifth product and method of use, requires a plant with mutated pIPAC gene and a method of making it not required by any other group.